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PHYSIOLOGIC STUDIES DURING HIGH FLOW, NORMOTHERMIC, WHOLE BODY PERFUSION

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WHOLE BODY perfusion for open intracardiac operations may be accomplished by a variety of techniques. Experience has led to the evolution of the system of high flow, normothermic perfusion which has been employed in this institution and found to be clinically satisfactory. The purpose of this study is to document the effect of such a perfusion upon certain physiologic variables in the perfused subject.

MATERIAL

During the last 2 weeks of August, 1958, 3 patients having acyanotic congenital heart disease were selected for study from the operative schedule of the Mayo Clinic.

Case 1 was that of a 10-year-old girl whose only symptom was easy fatigability. She weighed 36 kilograms and had a body surface area of 1.24 square meters. There was no precordial thrill, and the systolic murmur was only moderately loud. The heart was not enlarged. Cardiac catheterization performed elsewhere had indicated the presence of both atrial and ventricular septal defects. At operation on Aug. 19, 1958, an atrial septal defect was re-

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paired, but ventriculotomy and careful search revealed an intact ventricular septum. Her recovery was uneventful, and she was dismissed from the hospital 9 days later. A very faint residual systolic murmur could be heard.

Case 2 was that of a 9-year-old boy who had had fatigability and dyspnea on exertion throughout life. He weighed 41 kilograms, and his surface area was 1.24 square meters. His heart was overactive. He had a precordial thrill and an extremely loud systolic murmur. The heart was enlarged and the pulmonary vascular markings prominent. At operation on Aug. 26, 1958, the right ventricular systolic pressure was 45 mm. Hg. A typical high ventricular septal defect was identified and repaired by direct suture. His recovery was uneventful and he was dismissed from the hospital 11 days later, with no residual murmur audible.

Case 3 was that of a 9-year-old boy who had been slow to gain weight and who always seemed tired in spite of limited activities. He weighed 23 kilograms, and his surface area was 0.92 square meter. There was no precordial thrill, but a harsh systolic murmur and a markedly accentuated second pulmonic sound were present. The heart and pulmonary-artery segment were large at the time of operation (Aug. 28, 1958), and the right and left ventricular pressures were equal. A large patent ductus was identified and doubly ligated. A typical high ventricular septal defect was repaired by direct suture. Following perfusion, the right ventricular systolic pressure was normal (30 mm. Hg). The postoperative course was smooth, and the patient was dismissed from the hospital in 12 days, at which time no murmurs could be heard, although the second pulmonic sound remained somewhat accentuated.

METHOD

Anesthesia was induced with thiopental sodium and maintained with a mixture of 70 per cent nitrous oxide and 30 per cent oxygen at high flows, augmented as required with small doses of succinylcholine administered intravenously. Exposure for the operation was obtained through a bilateral anterior thoracotomy. Cannulation methods were those described previously.[1] A Gibbon-Mayo pump-oxygenator was used.[2, 3]

The rate of blood flow during perfusion was anticipated on the basis of previous experience, utilizing a system of perfusion wherein the rate of blood flow was controlled entirely by the rate of venous return. That experience indicated that when venous cannulation is perfect, and the patient normothermic, the perfusion rate is approximately 2.4 L. per minute per square meter of body surface[4] in the small child, diminishing to 2.0 L. per minute per square meter for an adult. Therefore, for children of the size selected for the present study, a flow of approximately 2.3 L. per minute per square meter of body surface was anticipated.

The pump which propels venous blood to the top of the oxygenator (the oxygenator pump) was set before the perfusion to deliver blood at this rate. The output of the arterial pump is regulated by level-sensing devices to equal the rate of venous blood return from the patient, up to a maximum that equals the output of the oxygenator pump. Venous return exceeding this volume per

minute accumulates and is sequestered in the venous reservoir and such blood is called "venous reservoir excess." Such excess usually accumulates after the heart is opened and the intracardiac blood is aspirated, and is thought in the main to represent central blood volume. If venous return should diminish later in the perfusion as a result of surgical hemorrhage, the excess blood in the venous reservoir will be returned automatically by the machine to the circulation. Under these circumstances, transfusion of a similar amount of blood will be required at the end of the perfusion when the central compartment is refilled.

There was no recirculation of blood through the oxygenator during total perfusion. A gas mixture consisting of 10 L. of oxygen and 0.2 L. of carbon dioxide was passed through the oxygenator each minute.

Normal body temperature is maintained in the perfusate by incorporating in the pump-oxygenator a heat exchanger of the type developed by Brown and his colleagues.[5] The oxygenator pump moves blood through the heat exchanger before it reaches the oxygenator.

Body temperature was measured by means of a thermistor passed transnasally into the mid-esophagus.

Venous pressure was measured by a plastic needle placed percutaneously into the left external jugular vein and by another placed in the right saphenous vein at the ankle. These were connected by nylon tubing to strain-gauge manometers which activated appropriate apparatus for permanent recording of the pressure tracings on photographic paper.[6] Similarly, arterial pressures were recorded by means of a small catheter passed 6 inches proximally through a needle placed percutaneously into the right femoral artery. Appropriate measurements were then made from the developed photographic paper. The mean venous pressure is here considered to be the average of the external jugular and the saphenous mean pressure.

A tachometer that measured the rate of rotation of the arterial pump recorded on the same photographic paper. From this information, the rate of blood flow through the extracorporeal circuit was determined. The output of the arterial pump was calibrated following each perfusion against pressures equal to those occurring during perfusion in the arterial line leading to the patient. The pressures generated in this arterial line were measured by a manometer system which is connected by a side arm to the arterial line.

Values for total peripheral resistance expressed in dynes seconds centimeters^{-5} were obtained by application of the formula:

$$\text{total peripheral resistance} = \frac{(\text{mean arterial} - \text{mean venous pressure in mm. Hg}) \times 1{,}332 \times 60}{\text{blood flow in liters per minute} \times 1{,}000}.$$

Blood samples used in the study of acid-base balance were drawn from an artery of the patient or the arterial line of the machine into sterile syringes, the dead space in the syringes having been filled with undiluted heparin solution which prevented clotting and enabled the procurement of blood samples free of air bubbles. The syringes were immediately capped and placed in ice,

and the samples were analyzed without delay for plasma carbon dioxide content, plasma pH, and erythrocytic volume percentage (hematocrit reading). Plasma carbon dioxide was determined on blood centrifuged after the method of Davenport[7] and analyzed by the method of Van Slyke and Neill.[8] Plasma pH was determined in a glass electrode assembly (Cambridge research model pH meter) enclosed in a circulated water jacket and maintained at 37° ± 0.1° C. For hematocrit determinations, blood was centrifuged in Wintrobe-Magath tubes at 1,500 revolutions per minute for 20 minutes. From these data, values for the partial pressure of carbon dioxide in the plasma and for the buffer base in whole blood were derived from the nomogram of Singer and Hastings.[9]

At about the mid-point of each perfusion, samples of whole blood were obtained from the venous and arterial lines of the bypass apparatus for the determination of oxygen content and oxygen capacity by the method of Van Slyke and Neill.[8] Oxygen consumption was then calculated from the formula: oxygen consumption = blood flow rate × (arterial blood – venous blood oxygen content). The error in this determination, resulting from the fact that bronchial arterial blood flow returns directly to the heart, is estimated to be negligible in these patients.

Oxygen tension of arterial blood was determined by the polarographic method,[10*] utilizing a sterile Clark oxygen electrode introduced directly into the flowing blood column in the arterial line of the bypass apparatus.

Percentage saturation of hemoglobin with oxygen was calculated after correcting for dissolved oxygen by dividing the oxygen content of the sample by its oxygen capacity. Dissolved oxygen content in the arterialized samples was calculated from two factors: the oxygen tension (pO_2) observed at the appropriate oxygen electrode at the time the sample was withdrawn, and the solubility coefficient for whole blood (0.023 c.c. of oxygen per cubic centimeter of solution at a pO_2 of 760 mm. Hg at 37° C.).[11] In the samples of venous blood, dissolved oxygen content was assumed to be 0.12 volume per 100 c.c. (that is, having a pO_2 of 40 mm. Hg).

RESULTS

Figs. 1, 2, and 3 record the arterial and venous pressures, flow rates, total peripheral resistances, venous reservoir excesses, and transfusions required during the perfusions in the 3 patients, respectively.

Mean arterial blood pressure dropped significantly (10 to 30 mm. Hg) at the time perfusion was begun, but during perfusion there was a definite small increase in the mean arterial pressure in 2 of the 3 cases. Total peripheral vascular resistance also increased during the period of perfusion in these 2 patients, but dropped significantly in all 3 patients at the instant cardiac asystole was relinquished.

The mean venous blood pressure remained essentially constant throughout each of the perfusions. The rate of blood flow during total perfusion was likewise constant in each of the cases, being approximately 2.3 L. per minute per

*These determinations were made by Dr. Manly Levin during the course of more extensive studies relating to blood oxygen tensions during perfusion.

square meter of body surface. The excess volume of blood above that which was required to maintain these blood flows was automatically withdrawn from circulation into the venous reservoir, as is also demonstrated by the graphs. During intracardiac repair the attendant surgical blood loss led not only to the gradual automatic return of this sequestered blood to the circulating volume but also required the transfusion of additional heparinized blood, amounting to about 600 c.c. in each instance.

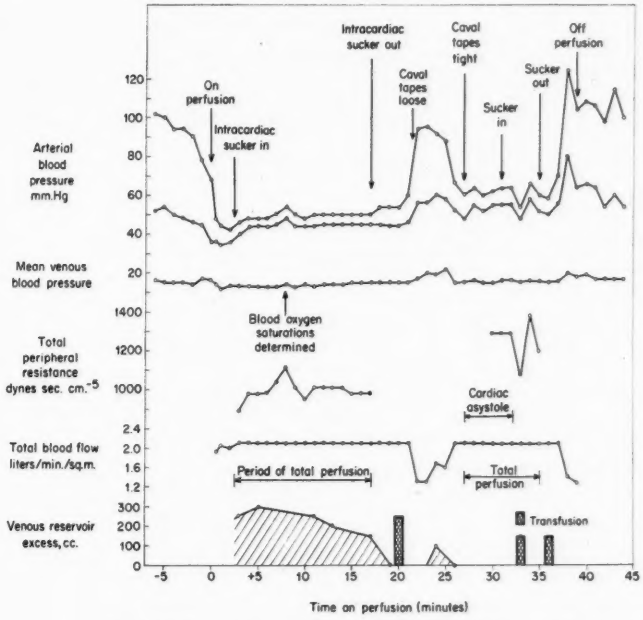

Fig. 1.—Hemodynamic data recorded during perfusion in Case 1.

In Table I are recorded the sizes of the arterial and venous cannulas used in the three patients, together with the blood flow rates employed, and the pressures that developed on either side of the cannulas. From this information, the pressure gradients across the cannulas were computed. For the venous cannulas this gradient varied from 20 to 26 mm. Hg, and for the arterial, from 35 to 80 mm. Hg.

TABLE I. CANNULA SIZE AND PRESSURE GRADIENT

		VENOUS CANNULAS				ARTERIAL CANNULAS			
CASE	FLOW (L./MIN.)	INTERNAL DIAMETER (INCHES)	VENOUS PRESSURE*	VENOUS RESERVOIR PRESSURE*	APPROX. GRADIENT*	INTERNAL DIAMETER (MM.)	ARTERIAL PRESSURE*	LINE PRESSURE*	GRADIENT*
1	2.6	5/16	13 to 16	−3 to −10	20	5.4	45-55	100-125	60-70
2	3.0	5/16	19 to 25	−3 to −10	26	5.4	45-85	105-160	60-80
3	2.1	5/16	13 to 19	−3 to −10	20	6.4	55-65	85-100	35-40

*In millimeters of mercury.

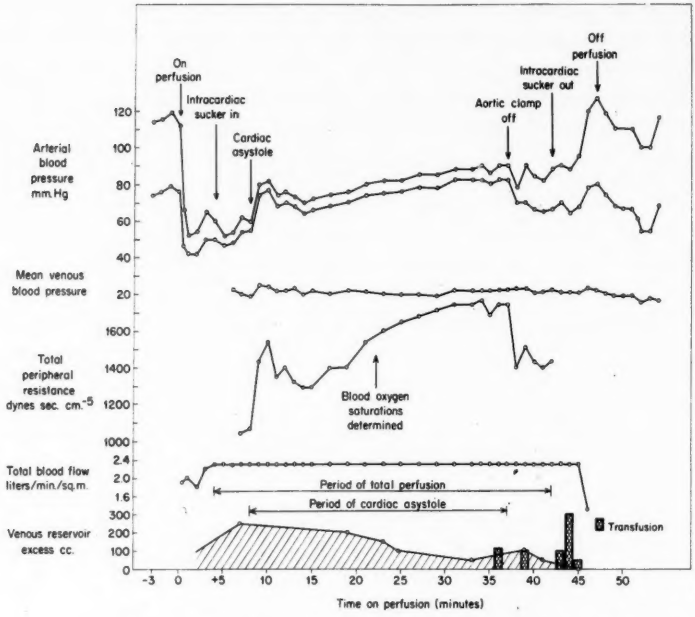

Fig. 2.—Hemodynamic data recorded during perfusion in Case 2.

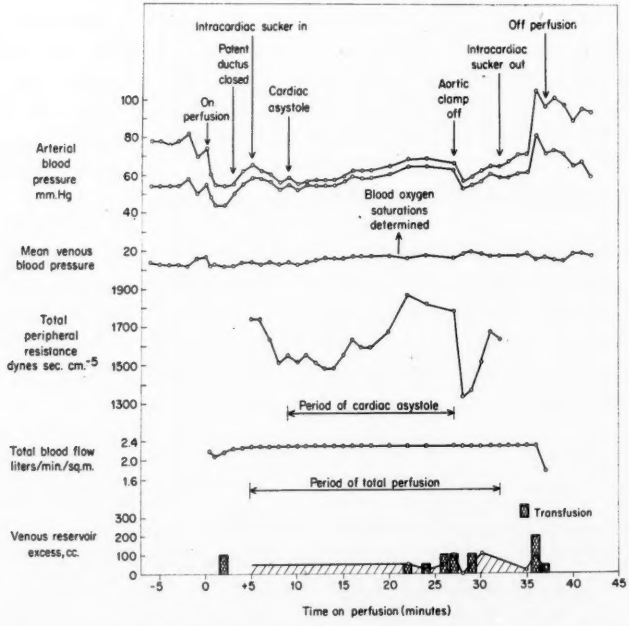

Fig. 3.—Hemodynamic data recorded during perfusion in Case 3.

Fig. 4 records the esophageal temperatures in each of the 3 cases. Although there was considerable variation in body temperature both before and after perfusion in these patients, the arterialized blood was constantly maintained during perfusion within the range of 36.5° to 37.5° C. After the beginning of perfusion, body temperature quickly equilibrated with the temperature of the perfusate.

Table II and Figs. 5, 6, and 7 record the acid-base balance that occurred throughout the operative procedure. It will be noted that the tension of carbon dioxide in the blood of the patients was markedly reduced by the hyperventilation associated with anesthesia and controlled respiration. Although some reduction in blood buffer base occurred during the course of anesthesia and operation, indicating accumulation of acid metabolites, the blood remained alkalotic owing to the overcompensation of hypocapnia. As perfusion is begun,

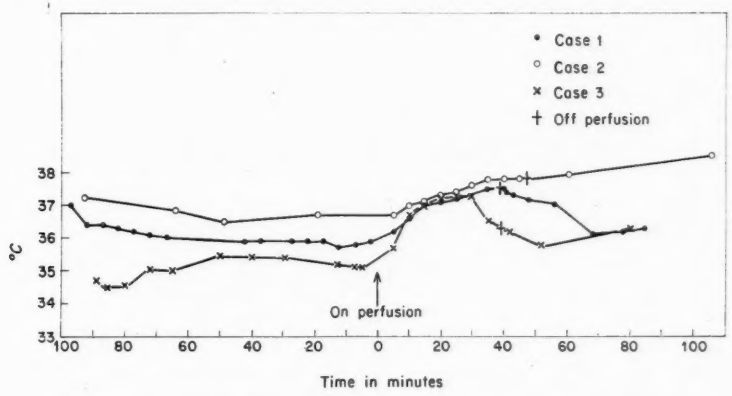

Fig. 4.—Esophageal temperature of the 3 patients during operation.

mixing of the blood of the patient and the blood in the apparatus occurs. This mixing has been indicated by the cross-hatched zones on the graphs. The value for buffer base, which represents an accurate index to metabolic factors affecting acid-base balance,[9] dropped slightly during two of the three perfusions, and climbed in the third.

Blood for the final determination relating to acid-base balance was drawn just after completion of the operation, following extubation of the patient, and some time after spontaneous respiration had been resumed. This accounts for the high concentration of carbon dioxide and low pH at that time, but is not indicative of increased metabolic acidosis, as is evident from the stable level of buffer base. Although no determinations were made between the time of completion of perfusion and the time of completion of anesthesia, the dotted lines on the graphs are indicative of the supposition that resumption of controlled hyperventilation following perfusion again caused reduction in the partial pressure of carbon dioxide in the blood.

The percentage saturations of hemoglobin in venous blood returning from the patient and in arterial blood returning to him at about the mid-point of the

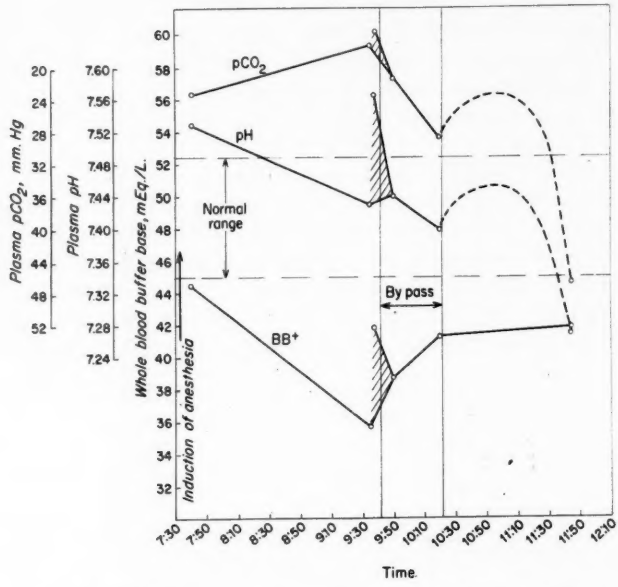

Fig. 5.—Acid-base balance occurring throughout the operative procedure in Case 1.

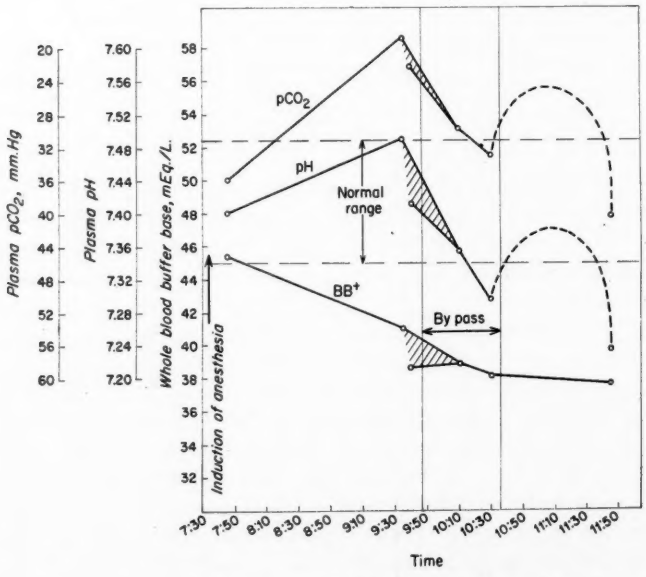

Fig. 6.—Acid-base balance occurring throughout the operative procedure in Case 2.

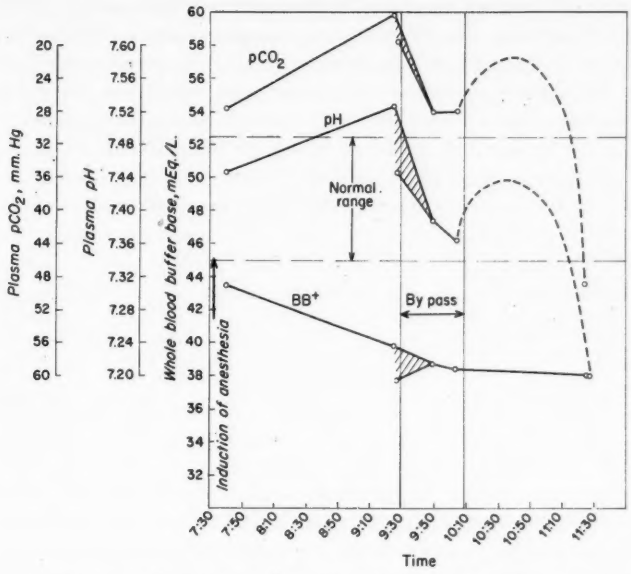

Fig. 7.—Acid-base balance occurring throughout the operative procedure in Case 3.

TABLE II. ACID-BASE BALANCE

CASE	SAMPLE*	HEMATOCRIT READING (RBC VOL. %)	CO_2 (mM/L.)	PLASMA pH	BUFFER BASE (mEq./L.)	pCO_2 (MM./Hg)
1	1	38.0	S† 19.85	7.528	44.5	23.4
	2	36.5	S 11.51	7.429	35.7	17.2
	3	42.0	S 13.88	7.545	41.7	15.7
	4	39.0	b† 12.41	7.438	38.8	21.4
	5	—	S 15.26	7.397	41.2	28.8
	6	40.0	S 19.51	7.267	41.8	47.0
2	1	43.0	S 22.82	7.400	45.3	36.0
	2	42.5	S 14.65	7.489	41.0	19.0
	3	—	S 14.63	7.410	38.6	22.2
	4	37.5	b 14.75	7.351	38.8	30.0
	5	41.0	S 16.87	7.295	38.0	33.0
	6	40.5	S 18.09	7.233	37.6	40.8
3	1	39.5	S 19.71	7.447	43.5	27.7
	2	39.0	S 13.39	7.526	39.8	16.3
	3	35.0	S 13.89	7.445	37.7	19.7
	4	37.5	b 14.48	7.386	38.7	27.9
	5	37.5	S 16.36	7.363	38.4	28.0
	6	44.0	S 20.37	7.200	38.0	49.0

*Identification of samples (arterial blood):

1. From patient just after induction of anesthesia.
2. From patient just prior to onset of perfusion.
3. From machine just prior to onset of perfusion.
4. From machine during perfusion.
5. From machine just prior to termination of perfusion.
6. From patient at completion of operation just after extubation of patient.

†S = plasma; b = whole blood.

perfusion are recorded for each of the cases in Table III. The average oxygen saturation of venous blood was 68 per cent, and complete arterialization was routinely accomplished by passage of the blood through the oxygenator. In two perfusions the hemoglobin of the arterial blood was completely saturated with oxygen, but excessive quantities of oxygen were not present in physical solution as demonstrated by satisfactory levels of oxygen tension (not in excess of 230 mm. Hg). Oxygen consumption during perfusion varied among the 3 cases from 100 to 162 c.c. per minute per square meter of body surface.

TABLE III. OXYGEN TRANSPORT DURING PERFUSION

CASE	FLOW (L./MIN. /SQ. M.)	VENOUS BLOOD CONTENT (VOL. %)	VENOUS BLOOD CAPACITY (VOL. %)	VENOUS BLOOD SAT. (%)	ARTERIAL BLOOD CONTENT (VOL. %)	ARTERIAL BLOOD CAPACITY (VOL. %)	ARTERIAL BLOOD SAT. (%)	ARTERIAL BLOOD pO_2 (MM. Hg)	O_2 CONSUMPTION (C.C./ MIN./SQ. M.)
1	2.1	11.39	16.14	72	15.58	16.14	97	230	100
2	2.4	10.32	16.27	64	16.77	16.27	100+	135	162
3	2.3	11.49	16.69	69	17.06	16.69	100+	190	140

COMMENT

With the flow rates utilized in the system of perfusion here studied, mean arterial pressure at the onset of perfusion was subnormal. A tendency to gradual increase in peripheral vascular resistance resulted in a similar tendency for gradual elevation of mean arterial pressure during perfusion, so that in 1 patient (Case 2) it was near normal at the end of the perfusion. In a previous study reported from this clinic,[12] during perfusions with lower rates of blood flow, similar changes in arterial pressure and resistance were noted. Dodrill and colleagues[13] noted the same phenomenon, and Mendelsohn and associates[14] found subnormal mean arterial blood pressures during perfusion.

It has been amply demonstrated in dogs[15-18] that arterial blood pressure during perfusion is closely related to blood flow rates. On the basis of the arterial blood pressures maintained during the perfusions of the present study, the flow rates utilized (approximately 2.3 L. per square meter of body surface per minute) might be assumed to be less than the cardiac output of the anesthetized patient prior to perfusion. However, data for comparison of peripheral resistance before and during perfusion in these patients are not available and it is therefore not possible to eliminate reduction of peripheral vascular resistance during perfusion as being etiologic in the lowering of arterial pressure.

A steady rate of blood flow in this system of perfusion is dependent upon free and unobstructed venous return from the patient, as is accomplished by the use of the largest possible venous cannulas. This in turn has resulted in the nearly steady levels of venous pressure encountered during these perfusions. Venous cannular obstruction would result in sequestration of blood in the obstructed venous bed, with resultant unaccountable loss of circulating blood volume and increased venous pressures.

The partial pressure of carbon dioxide during heart-lung bypass is largely controllable in most systems of perfusion through alteration in the rate of ventilation of the oxygenator and in the fractional concentration of carbon

dioxide in the gas passing through the oxygenator. In the perfusions being studied, the partial pressure of carbon dioxide in the arterialized blood was routinely maintained at levels that were lower than normal. This seems desirable, since the hypocapnia tends to prevent spontaneous respiratory motion by the patient, yet is probably not sufficiently severe to cause extensive reduction of cerebral blood flow.[19]

The development of mild metabolic acidosis during general anesthesia is usual.[20] Further progression of metabolic acidosis should not occur during perfusion if adequate flow rates of fully oxygenated arterial blood are employed.[21] The present studies indicate that this system of perfusion causes no significant increase in metabolic acidosis above that occurring during preperfusion anesthesia.

Oxygen consumption before and after perfusion has not been determined in clinical cases, and control values for comparison with oxygen-consumption data during perfusion are therefore not available. The average oxygen consumption of the anesthetized patients in this study during perfusion is somewhat lower than that occurring under waking basal conditions,[22] but is comparable to the oxygen-consumption values found during high flow perfusions under experimental conditions by several investigators.[15-18] Available data may be interpreted as indicating that oxygen uptake of a subject on perfusion increases with increasing perfusion flow rates only to a certain point, beyond which it remains unchanged with further increases in flow. At this point, the rate of blood flow probably results in perfusion of the entire body, rather than limited parts of it. Further increases of flow beyond this point, while resulting in no increase in oxygen uptake, result in a smaller arteriovenous oxygen difference. Oxygen uptake in these 3 cases averaged 134 c.c. per square meter per minute. In another study,[23] of a larger group of patients undergoing identical perfusions at this clinic, oxygen uptake averaged 130 c.c. per square meter per minute. This is comparable to the data available on oxygen uptake in anesthetized intact man.[20] From this it is concluded that the entire body is perfused by the system of perfusion used for the patients in this study. Venous oxygen saturations were found to be slightly lower during these perfusions than in intact resting man, implying a slightly subnormal average oxygen tension in the tissues.

The data gained from this study indicate that the body can be maintained in a nearly normal acid-base balance and hemodynamic state during interruption of cardiac function as permitted by the technique of normothermic, high flow, whole body perfusion here employed.

SUMMARY

Three patients requiring open-heart operations for repair of uncomplicated congenital heart lesions were selected for detailed physiologic study during operation. A system of perfusion utilizing a Gibbon-Mayo pump-oxygenator and a steady rate of blood flow of approximately 2.3 liters per square meter of body surface per minute was employed.

Mean arterial blood pressure became subnormal at the start of perfusion but tended to return progressively toward normal as the result of an increasing peripheral vascular resistance. Venous pressure remained steady and at a satisfactory level. Large size of the venous and arterial cannulas permitted minimal pressure gradients across them.

Metabolic acidosis of mild degree, compensated by respiratory alkalosis, occurred as a result of general anesthesia and manual hyperventilation, but perfusion caused no appreciable further metabolic acidosis.

Oxygen consumption during perfusion was found to be within normal limits for anesthetized man, and the oxygen saturation of venous blood hemoglobin was only slightly subnormal. The blood was fully arterialized by passage through the oxygenator.

The rate of blood flow employed during these perfusions is believed to be nearly as great as the rate of blood flow maintained by the functioning heart of the anesthetized patient.

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RESPIRATORY CHARACTERISTICS OF EXTRACORPOREAL PUMP-OXYGENATORS

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THE PUBLISHED REPORT of the symposium on *Extracorporeal Circulation*[1] clearly shows that mechanical pump-oxygenating systems can be operated successfully in a variety of ways. Several specific examples of this general statement might be mentioned. Various mixtures of oxygen and carbon dioxide can be used as the oxygenating gas. Various gas flow rates can be used. The gas can be prewarmed or left cold before entering the oxygenator, and it can be saturated with water or left dry. As yet the barometric pressure of a given locality has not limited the use of the pump-oxygenating systems. Finally, patients with widely varying metabolic rates can be perfused.

The variety of operating methods in current use is so great that the unwary might conclude that the variables mentioned above are unimportant. He might even be led to choose one operating feature from successful center A, another operating feature from successful center B, etc. No doubt, he would be surprised to view his own catastrophic results when he had chosen the best features of each of the best cardiac centers. The above is probably a ludicrous example, but it should serve to emphasize the point that extracorporeal pump-oxygenating machines are complex multifactorial systems that are finitely influenced by each of the factors alluded to in the previous paragraph. A change in any one of these factors changes the partial pressures of oxygen and carbon dioxide in the gas phase of the oxygenator and, hence, of the blood.

The purpose of the present paper is to interrelate in quantitative terms the factors which define the respiratory characteristics of the artificial heart-lung apparatus when connected to a metabolizing organism. This will be done in an abstract or theoretical form. The first problem encountered, in writing such a paper, is choice of tools to be used for the presentation. Words are poorly suited to the function of communicating abstract, quantitative ideas. Equations often bring about such a condensation of thought that functional interrelations are lost. Graphic analysis or nomography is a tool that is especially suited to this type of analysis and is the method used in the present paper. Henderson[4] was the first to apply this method to biologic systems.

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Rahn and Fenn[6] have used the method more recently to analyze the complexities of aviation physiology. The present paper utilizes many of the types of graphs developed by Rahn and Fenn. If the reader desires a rigorous development of the graphs used here, he is referred to their comprehensive monograph.

The present analysis is divided into five sections so that the reader can focus his attention more sharply on specific goals. The first section is a glossary of the symbols used. These symbols may at first appear cumbersome, but they conform to the standard symbols outlined in the symposium for the "Standardization of Definitions and Symbols in Respiratory Physiology."[5] The second section defines those factors which determine the partial pressures of oxygen and carbon dioxide in the gas phase of the oxygenator. The third section defines those factors which determine the partial pressures or tensions of oxygen and carbon dioxide in the blood that is leaving the oxygenator. The fourth section develops the thesis that the proper perfusion rate is determined by the aerobic metabolism of the organism being perfused and, as a consequence of this, the factors which determine the venous blood oxygen tension are defined. Finally, these various factors are simplified, as shown in Fig. 16, to point out one possible combination of monitoring devices which can be used to perform an adequate perfusion. This is the system currently in use at the University of Colorado Medical Center, which is a product of the analysis in the present paper. In essence, Fig. 16 shows that the arterial tension of CO_2 can be adequately followed by the continuous monitoring of arterial pH, and can be controlled by varying either the concenteration of CO_2 or the rate of flow of gas through the oxygenator. The arterial O_2 tension can also be followed polarographically and can be controlled by varying the ratio of oxygen consumption of the patient to the blood flow rate. I hope that the above broad outline of the organization and goals of this paper will help the reader maintain perspective as he is led through the more tedious portions.

I. GLOSSARY OF SYMBOLS

P_{O_2}—Partial pressure or tension of oxygen (mm.Hg) without reference to phase.

Pa_{O_2} and $P\bar{v}_{O_2}$—tension of oxygen in arterial and mixed venous blood, respectively.

$P_{I_{O_2}}$, $P_{C_{O_2}}$, $P_{E_{O_2}}$—tension of oxygen in influent, oxygenating chamber, and effluent gases, respectively, i.e., the gas entering the oxygenator and the gas leaving the oxygenator.

F_{O_2}—the fraction that oxygen is of the total gas mixture.

C_{O_2}—the content of oxygen in blood (vols. %).

D_{O_2}—rate of diffusion of oxygen.

CO_2 or H_2O—may be substituted for O_2 in any of the above symbols without changing any meaning other than the reference gas.

$\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$—rates of oxygen consumption and carbon dioxide production, respectively.

$\dot{V}_C$—rate of total gas flow through the oxygenator.

$\dot{Q}_B$—Cardiac output or pump flow rate.
P_B—barometric pressure.
S_{O_2}—percentage saturation of hemoglobin with oxygen.
R—the ratio at which CO_2 exchanges with O_2.
R_B—the blood respiratory exchange ratio.
R.Q.—the ratio of carbon dioxide production to oxygen consumption—the respiratory quotient.
Sol.—solubility.
M.W.—molecular weight.
Ds—disc speed or revolutions per minute.

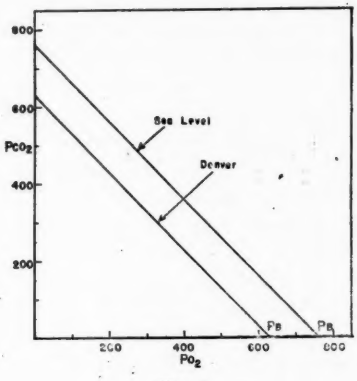

Fig. 1.

II. FACTORS CONTROLLING PARTIAL PRESSURES OF OXYGEN AND CARBON DIOXIDE IN THE GAS PHASE OF AN ARTIFICIAL OXYGENATOR

Most oxygenators operate with the gas phase at barometric pressure. In addition, most oxygenators handle only three gases: O_2, CO_2, and water vapor. Let us consider the consequences of these conditions. Dalton's Law states that the sum of the partial pressures of a mixture of gases is equal to the total pressure of the mixture. Since the total pressure is equal to the barometric pressure, we can write the following equation:

$$P_B = P_{O_2} + P_{CO_2} + P_{H_2O} \qquad (1)$$

Now let us turn to Fig. 1 to begin the graphic development. The ordinate is the partial pressure of CO_2 in mm. Hg. The abscissa is the partial pressure of O_2 in mm. Hg. The possible extremes that could exist, in the system described, can be represented by a point on the P_{O_2} axis at 760 mm. Hg and by a point on the P_{CO_2} axis at 760 mm. Hg. The first point would represent dry 100 per cent oxygen at sea level. The second point would represent dry 100 per cent carbon dioxide at sea level. A straight line drawn between these two points completes a triangle which encloses all possible combinations of P_{O_2} and P_{CO_2} that can exist at a barometric pressure of 760. Denver, Colorado, is at an altitude of 5,280 feet and has an average P_B of approximately 630 mm. Hg. The consequences of this fact are shown on Fig. 1 as the Denver line.

If we further limit the conditions under which the oxygenator operates, a more precise definition of P_{O_2} and P_{CO_2} can be achieved, since at 37° C., water vapor pressure is 47 mg. If the oxygenating gas is saturated with water at 37° C., before entering the chamber, we can say,

$$P_{I_{H_2O}} = P_{C_{H_2O}} = P_{E_{H_2O}} = 47 \text{ mm. Hg} \quad (2)$$

Substituting this into equation (1) and rearranging we have:

$$P_B - 47 = P_{O_2} + P_{CO_2} \quad (3)$$

or, for Denver:

$$583 = P_{O_2} + P_{CO_2} \quad (4)$$

This equation is expressed graphically in Fig. 2. We begin with the Denver P_B line, subtract 47 from each of the coordinate points, and join them by a line. This line, R, is the respiratory exchange ratio line. If one substitutes

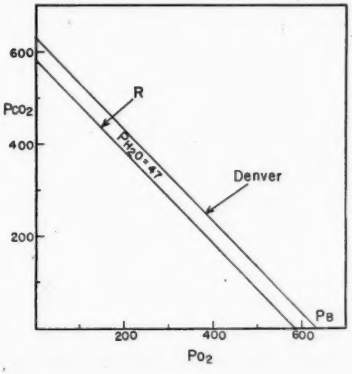

Fig. 2.

any value between zero and 583, for P_{O_2} in (4), he can solve for P_{CO_2}. If such points are plotted on Fig. 2, it will be found that all points lie on the R line. Therefore, the R line expresses all possible combinations of P_{O_2} and P_{CO_2} that can exist in the gas phase operating under the conditions specified (5,280 feet, water saturated, at 37° C.). If the operating temperature is less than 37° C., the R line must be changed to correspond to the new P_{H_2O} value.

The next subject we shall consider is the factors that define the positions of the P_I, P_C, and P_E points on the R line. The determination of the P_I point is the simplest and shall be considered first.

Currently, most perfusionists use as an oxygenating gas either pure oxygen or a mixture of oxygen and carbon dioxide. Thus, the minimum of carbon dioxide used is zero, and an average is about 3 per cent. The maximum, to our knowledge, is 6 per cent. These combinations in the influent gas mixture can be plotted on the R line of the $P_{O_2} - P_{CO_2}$ diagram as shown in Fig. 3. These points represent, in ascending order, zero, 3, and 6 per cent carbon dioxide. Their positions on the graph are determined solely by the fractional concentrations of the influent oxygen and carbon dioxide.

Now let us consider the definition of the Pc and PE points. In the lungs, the magnitude of the difference between the alveolar point and the expired point on the R line is a direct function of the dead space. In the disc oxygenator the Pc point is analogous to the alveolar point in the lungs, and the PE point is analogous to the expired point. The oxygenator has no dead space analogous to that in the lungs, so that in the oxygenator Pc = PE.

Now we can proceed to analyze the two factors which define the difference between the PI and Pc points on the R line. Fig. 4 is a $P_{O_2} - P_{CO_2}$ diagram with an expanded scale so that the influence of these two factors can be more

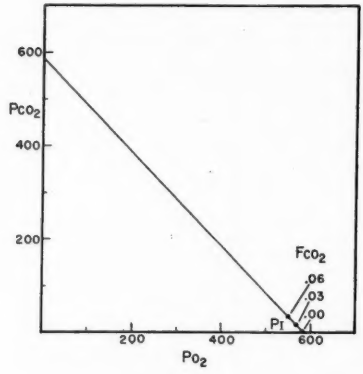

Fig. 3.

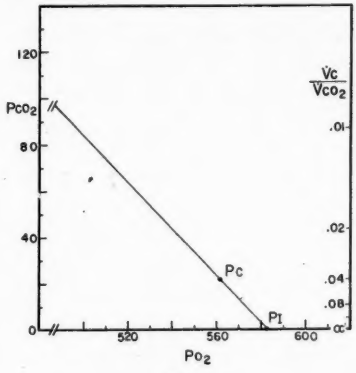

Fig. 4.

readily appreciated. The reader will note that the PI point is that of an oxygenator using pure oxygen. When this is true, the Pc point is completely independent of oxygen consumption, because removal of oxygen by the blood merely reduces the rate of flow of oxygen at the effluent end. However, as CO_2 escapes from the blood phase to the gas phase of the chamber, $P_{c_{CO_2}}$ increases and from (4) $P_{c_{O_2}}$ decreases. Or, from Fig. 4, the Pc point moves up the R line as a function of the rate of addition of CO_2 which, in a steady state, is the rate of CO_2 production by the organism being perfused. This ascent along the R line can be reversed by increasing the rate of total gas flow through the oxygenator. In essence, then, the difference between the PI point and the Pc point is determined solely by the ratio of the total gas flow through the chamber to the CO_2 production, $\dot{V}c/\dot{V}co_2$. Note that the right ordinate of the graph is expressed in these ratio units. For example, if an individual is producing 125 c.c. of CO_2 per minute, and there is an oxygen flow through the oxygenator of 5 L. per minute, he has a $\dot{V}c/\dot{V}co_2$ of 0.04. His position on the R line is represented as point *C* on Fig. 4. This would yield a $P_{c_{CO_2}}$ of 22 and $P_{c_{O_2}}$ of 561. If the gas flow remained constant and the CO_2 production increased to 250 c.c. per minute, the $\dot{V}c/\dot{V}co_2$ would decrease to 0.02 and the P_{cCO_2} would rise to 44. Having achieved this point the $P_{c_{CO_2}}$ could be returned to the original point, *C*, by increasing the gas flow to 10 L. per minute, thus restoring the ratio to 0.04.

Fig. 5 is like the preceding diagram except in this case the influent gas contains 3 per cent CO_2. Note that having CO_2 in the oxygenating gas mixture shifts the $\dot{V}c/\dot{V}co_2$ lines up so that the infinity ratio coincides on the Y axis with the PI point. Functionally, this means that for a given rate of CO_2 production, a higher rate of gas flow must be maintained to hold the chamber gas concentrations at a Pc_{CO_2} of 22 and a Pc_{O_2} of 561.

Now let us briefly retrace our steps before proceeding to the next section. We have shown that the R line is dependent upon the barometric pressure, saturation of the gas with water, and the temperature at which saturation is achieved. The R line, thus derived, describes all possible combinations of P_{O_2}

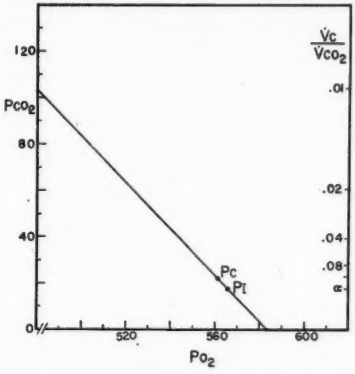

Fig. 5.

and P_{CO_2} that can exist in the gas phase of an oxygenator which contains only O_2, CO_2, and H_2O in the oxygenating mixture. The difference between the PI and Pc points on the R line is determined by the ratio of the rate of gas flow through the oxygenator to the rate of the CO_2 production, and since in the disc oxygenator there is no dead space, Pc = PE.

III. FACTORS DETERMINING THE P_{O_2} AND P_{CO_2} OF THE ARTERIAL BLOOD

If the oxygenating system is efficient enough to establish equilibrium between the gas phase and the blood phase, as is essentially the case in human lungs, the arterial tensions of O_2 and CO_2 will be identical with those of the chamber gas. To the extent that the oxygenator is not 100 per cent efficient, the arterial point will differ from point C on the $P_{O_2} = P_{CO_2}$ diagram. This difference, however, will conform to a definite ratio of P_{CO_2} to P_{O_2}.

Comroe[2] states that the ratio of the diffusion of CO_2 to O_2 is defined by:

$$\frac{\dot{D}o_2}{\dot{D}co_2} = \frac{Sol._{O_2}}{Sol._{CO_2}} \sqrt{\frac{M.W._{CO_2}}{M.W._{O_2}}} .$$

At 37° C., the gas phase–blood phase gradient will be approximately 20 times as great for O_2 as for CO_2. Fig. 6 expresses this relationship graphically. On

this graph we have returned to the original scale on the $P_{O_2} - P_{CO_2}$ diagram. If, by means described in a previous section, the chamber tensions of the gases in the gas phase are held so that $P_{C_{CO_2}}$ is 17 mm. Hg, the middle Pc point on the graph, one can draw a line from that point toward the P_{CO_2} axis with a slope of –1/20. This line describes all possible arterial blood tensions of O_2 and CO_2 that could exist with this Pc point. Three such lines are indicated on the graph. Note that the lines are parallel and that their intercept with the R line is determined by the Pc. These lines are called $O_2 - CO_2$ diffusion ratio lines ($\dot{D}_{O_2}/\dot{D}_{CO_2}$). It should be emphasized that the diffusion ratio lines have a slope of –1/20 only at 37° C., since a change of temperature does not affect the solubilities of the two gases proportionately. If the operating temperature is less than 37° the slope becomes smaller—at 15° C. it is approximately –1/25.

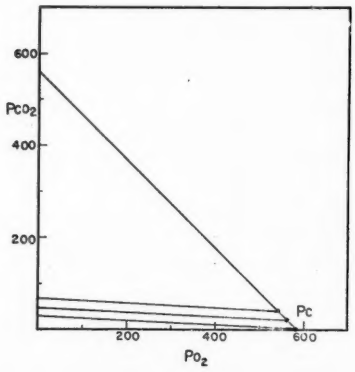

Fig. 6.

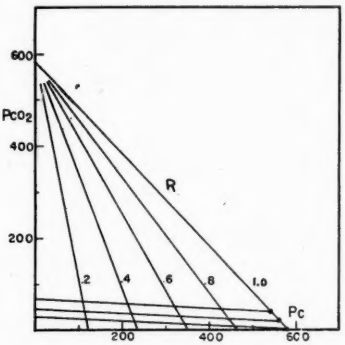

Fig. 7.

Now we must take up the question of the factors that define the position of the P_A point on its diffusion ratio line. Earlier it was stated that if any oxygenator is completely efficient, that is, if there is complete equilibration between the gas phase and the blood phase, the chamber gas point will be identical with the arterial blood point. If this argument is carried further, we can define the position of the arterial blood point in terms of the efficiency of the oxygenator. The efficiency of oxygenators can be defined in many ways. For present purposes, let us make the arbitrary definition that the equilibrating efficiency of an oxygenator is the fraction that $P_{a_{O_2}}$ is of $P_{c_{O_2}}$. For example, if the $P_{c_{O_2}}$ is 560 mm. Hg, and the $P_{a_{O_2}}$ is 100 mm. Hg, the equilibrating efficiency of the oxygenator at that time is 100 divided by 560 or 0.179. Fig. 7 graphically expresses the equilibrating efficiency lines as radiating from the intercept of the R line on the P_{CO_2} axis. The reader will note that the fractional efficiency of 1.0 coincides with the R line. The diffusion ratio lines are given for $F_{C_{CO_2}}$ of 0.00, 0.03, and 0.06. The intercept of the diffusion ratio lines with the efficiency lines defines the tensions of CO_2 and O_2 of the arterial blood.

The equilibrating efficiencies of oxygenators vary from type to type. Indeed, the equilibrating efficiency of a given oxygenator may vary from moment to moment depending on the conditions of the perfusion. In simplest terms, however, the equilibrating efficiency of any oxygenating system is a function of the time during which a given surface area of blood is exposed to the chamber gas. Thus, for all types of oxygenators, the equilibrating efficiency is a partial function of the time required for the blood to flow through the oxygenating system. Obviously, if blood is flowing through an oxygenator very slowly a higher efficiency will be achieved. Other factors are peculiar to the type of oxygenator being used. For example, the equilibrating efficiency of the rotating disc oxygenator is varied by the size, shape, and number of discs as well as by the revolutions per minute of the discs and the turnover rate of the blood in the oxygenator. During any given perfusion, however, the equilibrating efficiency is determined primarily by the ratio of disc speed to blood flow rate, assuming the $P\bar{v}o_2$ is kept constant. As the disc speed increases, the

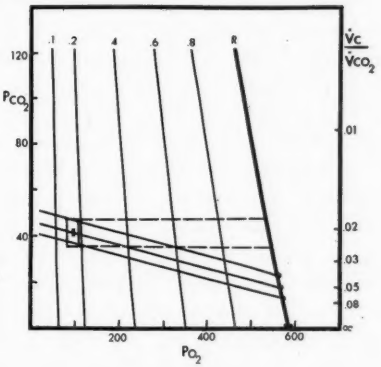

Fig. 8.

equilibrating efficiency increases; as the blood flow rate increases, the equilibrating efficiency decreases. The consequences of these relations will be mentioned after a description of the next graph.

To combine the graphs relating the control of Pc and the control of Pa, we need to change the P_{CO_2} scale slightly as in Fig. 8. The P_{O_2} axis is the same as that shown previously. The P_{CO_2} axis has been expanded so that its narrower biologically permissible limits can be observed more closely. Changing this axis makes the R line and the efficiency lines appear more vertical, their geometric slopes, however, are the same as shown on the previous graph. The same statements apply to the $\frac{\dot{D}o_2}{\dot{D}co_2}$ lines. The right-hand ordinate has a $\dot{V}c/\dot{V}co_2$ scale appropriately adjusted to the P_{CO_2} axis. The P1 point indicates that 100 per cent O_2 is the influent gas. The small rectangle in the left portion of Fig. 8 is the area of normal values. This area encompasses the range of values which occur in normal humans, as reported in the *Handbook of Biological Data*.[8]

Horizontal projections, from this rectangle, to the R line encloses an area which, for the sake of discussion, shall be referred to as the permissible area. The permissible area includes values of Pa_{O_2} and Pa_{CO_2} which can conservatively be stated to be safe for several hours.

The relationships defined by the graph of Fig. 8 reveal a number of interesting points. In order to maintain normal arterial tensions of the respiratory gases, the oxygenator must have a low equilibrating efficiency—between approximately 0.15 and 0.19. The O_2 to CO_2 diffusion ratio lines, which pass through the normal area, intercept the R line between 14 and 24 Pc_{CO_2}. This means that the CO_2 tensions in the effluent gas must be maintained between 14 and 24 mm. Hg, and the equilibrating efficiency must be kept between 0.15 and 0.19 if the arterial respiratory gas tensions are to be maintained in the normal area. These PE_{CO_2} values correspond to 2.5 and 4.1 per cent CO_2 when the oxygenator is operated under the conditions assumed. The graph also shows that to maintain this PE_{CO_2} or Pc_{CO_2} the ratio of the rate of gas flow to the rate of CO_2 production must be maintained between 0.06 and 0.036 if the oxygenating gas is 100 per cent O_2.

Another interesting point that the graph reveals might be worth mentioning. A change in efficiency results in a much larger change in the Pa_{O_2} than in the Pa_{CO_2}. Conversely, a change in Pc_{CO_2} has a greater effect on the Pa_{CO_2} than on the Pa_{O_2}. These facts enable the perfusionist to dissociate control of Pa_{O_2} and Pa_{CO_2} to a large extent. In the disc oxygenator, the efficiency, and, therefore, the PA_{O_2} can be controlled by the perfusionist's control of the disc speed—pump rate ratio. In the bubble oxygenator, the same can be accomplished by a variation in bubble size—the larger the bubbles the smaller the oxygenating efficiency. The Pc_{CO_2} and, therefore, the Pa_{CO_2} can be controlled by the perfusionist's alteration of the ratio of the rate of gas flow to the rate of CO_2 production, or by a change in the per cent of CO_2 in the influent gas. Either type of control can be used by the perfusionist. However, it is probably simpler to vary the rate of flow of oxygen, since this avoids the necessity of having two tanks of oxygenating gas with different fractions of CO_2, and of having mixing gauges which are accurate.

IV. FACTORS DETERMINING THE P_{O_2} AND P_{CO_2} OF THE VENOUS BLOOD

Now we must consider the interrelations of those factors which define the difference between the tensions of the respiratory gases in the arterial blood and in the venous blood, i.e., the difference between the Pa point and the $P\bar{v}$ points on the $P_{O_2} - P_{CO_2}$ diagram. Instead of going directly to the $P_{O_2} - P_{CO_2}$ diagram, however, we shall take a few intermediate steps of gentler intellectual grade. We shall first describe how a living organism solves this problem, and then we shall see how the artificial pump-oxygenator can be operated to mimic this solution.

One of the simplest approaches is via the Fick equation which states:

$$\dot{V}_{O_2} = \frac{\dot{Q}_B\,(Ca_{O_2} - C\bar{v}_{O_2})}{100} \qquad (6)$$

or that the total oxygen consumption of the body is equal to the cardiac output times the arterial-venous oxygen difference. This relationship can be graphically expressed as shown in Fig. 9. The ordinate of this graph is the rate of oxygen consumption, and the abscissa is the cardiac output. The lines radiating from the origin are the arterial-venous oxygen differences. Therefore, the slope of the relationship between the oxygen consumption and cardiac output is defined by the arterial-venous oxygen difference. The dots represent data obtained from a series of normal humans studied at this institution.[7] From this graph, one would conclude that variations in oxygen consumption amongst individuals are met by variations in cardiac output sufficient to maintain a normal $Ca_{O_2} - C\bar{v}_{O_2}$. It would seem, therefore, that one of the ideals of perfusion would be to deliver the rate of blood flow which meets the oxygen consumption

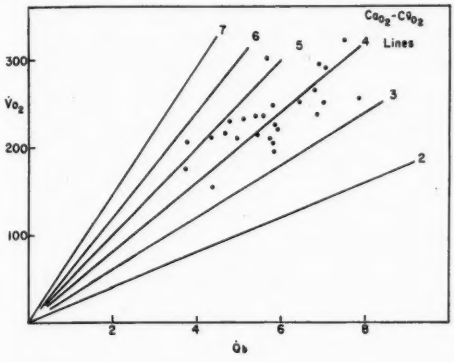

Fig. 9.

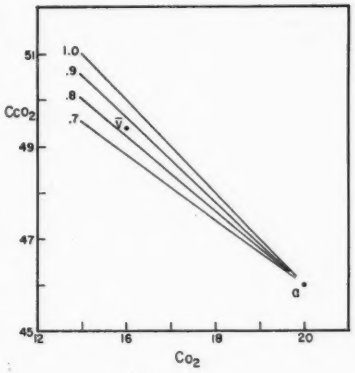

Fig. 10.

demands and maintains an arterial-venous oxygen difference between 5.5 and 3.5 vol. per cent. However, it would seem reasonable that circumstances could occur in which this ideal is achieved and yet have the organism in severe difficulty by not taking proper account of C_{O_2} transport. In order to include a consideration of CO_2, let us make another approach by means of the $C_{O_2} - C_{CO_2}$ diagram. Such a diagram can relate the contents of O_2 and CO_2 in the blood through the following equation,

$$R_B = \frac{C\bar{v}_{CO_2} - Ca_{CO_2}}{Ca_{O_2} - C\bar{v}_{O_2}} \qquad (7)$$

and in a steady state:

$$R_B = R.Q. \qquad (8)$$

The ordinate of Fig. 10 is the C_{CO_2} and the abscissa is the C_{O_2}.

The units for each coordinate are volumes per cent. If an individual has Ca_{CO_2} of 20 and Ca_{O_2} of 46, this can be graphed as point *a* on Fig. 10. The lines radiating from *a* are the R_B lines or the blood respiratory exchange ratio lines. When the individual is in a steady state, R_B is equal to R.Q., and the

R.Q., then, defines the RB line on which the $\bar{v}$ point must lie. The hypothetical points plotted are for an individual with Ca_{O_2} of 20, Ca_{CO_2} of 46, $C\bar{v}_{O_2}$ of 16, $C\bar{v}_{O_2}$ of 49, and R.Q. of 0.85.

One problem with this diagram is its failure to relate the factors which define where the $\bar{v}$ point will fall on its RB line. A slight addition to the graph, however, allows this to be done. The $Ca_{O_2} - C\bar{v}_{CO_2}$ can be estimated from Fig. 10 by simply determining the differences between the *a* point and $\bar{v}$ point on the graph. Then let us rearrange (6) to,

$$\frac{\dot{V}_{O_2}}{\dot{Q}_B} = \frac{Ca_{O_2} - C\bar{v}_{O_2}}{100} \tag{9}$$

and by the same reasoning we get,

$$\frac{\dot{V}_{CO_2}}{\dot{Q}_B} = \frac{C\bar{v}_{CO_2} - Ca_{CO_2}}{100} \tag{10}$$

Equations (9) and (10) can be added to (7) and (8) to obtain,

$$R.Q. = RB = \frac{C\bar{v}_{CO_2} - Ca_{CO_2}}{Ca_{O_2} - C\bar{v}_{O_2}} = \frac{\frac{\dot{V}_{CO_2}}{\dot{Q}_B}}{\frac{\dot{V}_{O_2}}{\dot{Q}_B}} \tag{11}$$

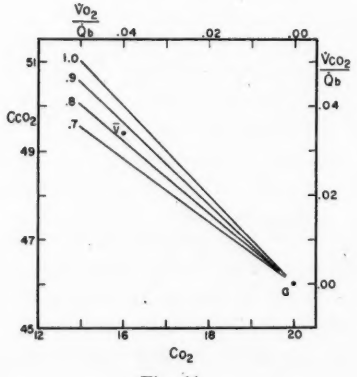

Fig. 11.

These relations can be added to Fig. 10 to obtain Fig. 11. The right ordinate and upper abscissa are the $\frac{\dot{V}_{CO_2}}{\dot{Q}_B}$ and the $\frac{\dot{V}_{O_2}}{\dot{Q}_B}$, respectively. This graph shows that the difference between the *a* point and the $\bar{v}$ point on the RB line is determined by the ratio of the rate of O_2 consumption to the cardiac output or the ratio of the rate of CO_2 production to the cardiac output. *We see again that the body adjusts the cardiac output to the metabolic needs of the individual. The same feat could be accomplished by the pump-oxygenator if the contents of the respiratory gases in blood could be continuously monitored. This would allow the perfusionist to adjust the rate of blood flow to the metabolic needs of the patient without knowing either. Unfortunately, however, such instrumentation is not presently available; therefore, another solution must be sought.*

Currently, pH, Pa_{O_2}, and $P\bar{v}_{O_2}$ can be monitored. Is it possible to derive a graph in these terms which would guide the perfusionist in achieving this adjustment of blood flow to metabolic needs? The next several graphs are steps in this derivation.

The relationships expressed in Fig. 11 on the Co_2 – Cco_2 diagram can also be expressed on the Po_2 – Pco_2 diagram. The form is not as convenient, because the dissociation of oxyhemoglobin is not linear. Let us recall the familiar oxyhemoglobin dissociation curve to mind and see how it can be expressed in a form that is more useful for present purposes. Fig. 12 shows the relationships amongst Po_2, Pco_2, and Co_2 in human blood at 37° C. It is of importance to mention, at this point, the known and unknown effects of hypothermia on these curves. It is well established that cold shifts the dissociation curve, of a given Pco_2, to the left. It is not clear from the literature what the Pco_2 has to be increased to in order to shift the curve back to the right. This important group of facts is not presently available to those who combine hypothermia and extracorporeal circulation. This is the subject of a current investigation in this laboratory. Now let us project a line horizontally from the Co_2 axis at 15 vols. per cent. The projected line is a line of constant Co_2. Note that it crosses each of the dissociation curves. These points can be plotted as tensions on the

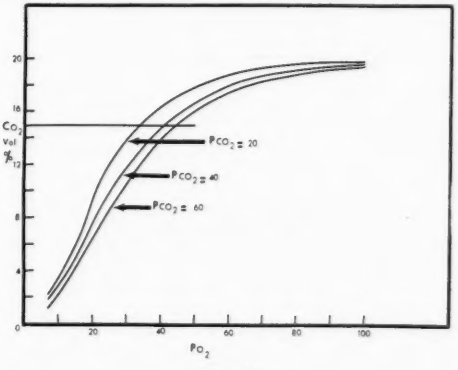

Fig. 12.

Po_2 – Pco_2 diagram and the points joined by a smooth curve, the constant oxygen content curve. Such dissociation curves are shown on the Po_2 – Pco_2 diagram of Fig. 13 for a Co_2 of 6, 10, 14, 15, and other values. The volumes per cent of each line is expressed at the top of the line. Now if any two of the three relationships mentioned above are known, a point representing Pa can be plotted which simultaneously shows the magnitude of Pa_{O_2}, Pa_{CO_2}, and Ca_{O_2}. Let "a" be the arterial point of a hypothetical individual. You will recall from Fig. 11 that the venous point is partially defined under these conditions by the ratio of the oxygen consumption of the individual to his cardiac ouput. You will recall further that this ratio is equal to the A-V oxygen difference (Ca_{O_2} – $C\bar{v}_{O_2}$). The $\frac{\dot{V}o_2}{Q_B}$ is indicated on Fig. 13 below the lines of equal oxygen content; whatever line "a" falls on will have infinity as the

value of this ratio. If the $Ca_{O_2} - C\bar{v}_{O_2}$ of the individual is in the normal range (3.5-5.5 vols. per cent) the $\frac{\dot{V}O_2}{\dot{Q}_B}$ must be between 0.0355 and 0.055 as seen in Fig. 9, and the venous point must lie somewhere between these lines. Where the venous point will lie with respect to the P_{CO_2} axis can be predicted from a knowledge of the C_{CO_2} of the blood.

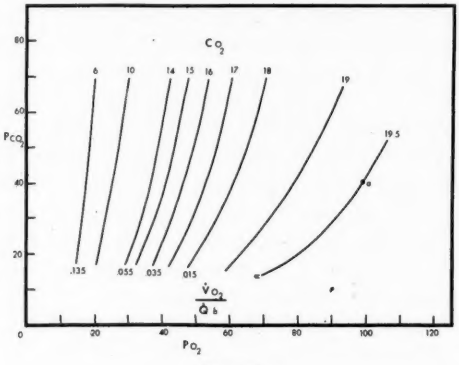

Fig. 13.

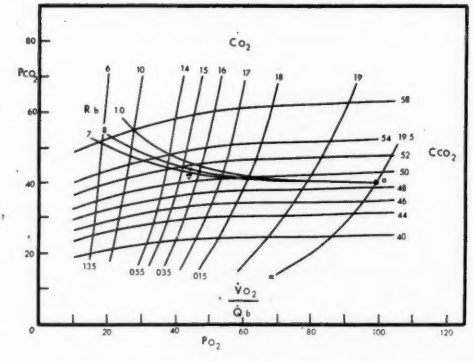

Fig. 14.

Let us relate the CO_2 content of the blood to the $P_{O_2} - P_{CO_2}$ diagram. This can be done, for blood with an oxygen capacity of 20 volumes per cent, by utilizing the quantitative relations of the Bohr effect as contained in the nomogram of Dill and his associates.[3] Fig. 14 is similar to Fig. 13 with certain additions. The lines coming up from the lower left-hand corner and extending horizontally almost parallel to the P_{O_2} axis are lines of equal CO_2 content of blood. With this addition it is now possible to draw in the R_B lines as was done on Fig. 11. The curved lines radiating from *a* are the R_B lines ranging from 1.0 to 0.7. It will be recalled that in a steady state the R_B lines are equal to the R.Q. of the individual.

The venous point described on the graph of Fig. 14 is therefore that in an individual with an R.Q. of 0.8 and a normal A-V oxygen difference of 4 vols. per cent. This individual then would have a C_{CO_2} of 51.5 vols. per cent, $P\bar{v}_{CO_2}$ of 44, and a $P\bar{v}_{O_2}$ of 44.

One interesting fact revealed by this graph is that if the arterial point is controlled along the P_{CO_2} and the P_{O_2} axes, the venous point would have to be controlled only along the P_{CO_2} axis, since large changes in R.Q. cause only small changes in $P\bar{v}_{CO_2}$. The control of the venous point along the P_{CO_2} axis is dependent on the ratio between the rate with which oxygen of the blood is being removed by the tissues to the CO_2 being added to the blood from the tissues or the RB. As mentioned earlier, however, at the present time we lack instrumentation to define adequately the arterial point along the P_{CO_2} axis. And, another difficulty with this form of graph is that CO_2 content, which allows one to depict the RB lines, is referable only to an individual with the specific oxygen capacity of the blood of 20 vols. per cent.

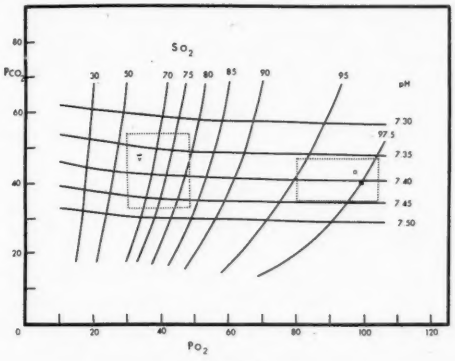

Fig. 15.

The relations depicted in Fig. 14 can be generalized and made more useful for the adaptation of the artificial pump-oxygenator *by changing the lines of equal oxygen content to lines of constant oxyhemaglobin saturation.* In addition, *the lines of constant carbon dioxide content can be changed to become lines of constant blood pH.* These relations are illustrated in Fig. 15 and allow us to fix the arterial point on the X axis by monitoring either the P_{O_2} or the per cent saturation of blood. The arterial point can be fixed with reference to the Y axis by continuous monitoring of the P_{CO_2} or the pH. The venous point can be fixed on the X axis by monitoring either the P_{O_2} or per cent saturation of the venous blood; and as we saw in the previous graph, it is unnecessary to fix the venous point on the Y axis. However, if such information were desired, this point could be fixed by monitoring either the venous pH or the venous P_{O_2}. Since instrumentation is currently under development for each of the four parameters related on Fig. 15, this graph becomes a most useful one in describing a physiologic perfusion. The choice of the two parameters to be monitored is left to the experience of the perfusionist.

An interesting point might be made in reference to the accuracy with which one must measure these parameters in order to perform as well as the body. The rectangles enclosed by dotted lines describe the normal values for P_{CO_2} and P_{O_2} that are listed in the *Handbook of Biological Data*.[8] The range of normal Pa_{O_2} is from 80 to 104 mm. Hg. If one recalls that the permissible range of Pa_{O_2} includes much higher tensions, it becomes apparent that if one chooses to monitor the Pa_{O_2} and maintain it at 100, he needs only to measure this parameter with an accuracy of plus or minus 20 per cent in order to maintain this value within acceptable limits. If one chooses to monitor the arterial point on the X axis by means of per cent saturation, it is apparent that no such gross instrumental error can be allowed. Similarly, the normal range of Pa_{CO_2} is from 45 to 47. Therefore, if one choses to fix the arterial point with respect to the Y axis by monitoring the Pa_{CO_2}, instrumentation that was accurate within plus or minus 15 per cent would do as well as the body. If he chooses to fix this point by monitoring pH, instrumentation that will have an accuracy of plus or minus 0.05 pH units is required. The normal range of $P\bar{v}_{O_2}$ is 30 to 48 mm. Hg. Again, if one chooses to monitor this point by means of P_{O_2} measurements, the accuracy required is not great—plus or minus 20 per cent will keep the venous point well within these limits. If one is using the venous saturation, more latitude is allowed for error here than in the arterial point. Finally, there is no need to fix the venous point with reference to the Y axis as was indicated by the relations drawn in the previous diagram.

V. ONE POSSIBLE ADAPTATION OF THESE STUDIES WHICH ADEQUATELY CONTROLS WHOLE BODY PERFUSION

Fig. 16 includes the key points of the previous graphs expressed in physiologic terms which would theoretically allow one to monitor adequately and control the arterial and venous points and to make appropriate adjustment to their change. Fig. 17 is the same graph expressed in terms of functions of the pump-oxygenator. The arterial point lies on the straight dotted line which is the $O_2 - CO_2$ diffusion ratio line. This line and, therefore, point *a* on the line moves in the upward direction with an increase in CO_2 production by the patient being perfused. The upward movement of *a* is impeded by an increase in the rate of flow of gas through the oxygenator. The slope of the line along which *a* moves up and down is that of an equilibrating efficiency of 0.18. Moreover, *a* can move along the $O_2 - CO_2$ diffusion ratio line by a variation in the efficiency. This efficiency during a perfusion with the disc oxygenator would allow *a* to be moved to the right by an increase in disc speed and it would move to the left when there was an increase in the rate of perfusion of the patient. If the device for measuring the Pa_{O_2} has an accuracy of ±20 per cent, the perfusionist can adjust the disc speed of the oxygenator so that the apparent Pa_{O_2} is 100 mm. Hg and know that the true Pa_{O_2} lies within the permissible range. The perfusionist would not vary the rate of blood flow by the pump in order to change the *a* point. As shall be seen later, the perfusionist is committed to deliver a rate of blood flow to the patient that maintains a normal $P\bar{v}_{O_2}$. If the perfusionist has a device that will continuously measure arterial blood pH to within ±0.05 pH units, he can vary the rate of flow of oxygen

through the oxygenator so that the apparent arterial pH is 7.40 and be assured that the arterial pH and P_{CO_2} are within the normal limits. With the arterial point fixed in this manner, the perfusionist knows that the venous point lies somewhere along the RB line that the patient is on at that particular time. The RB line indicated on Fig. 16 is that of 0.8, a reasonable fasting value.

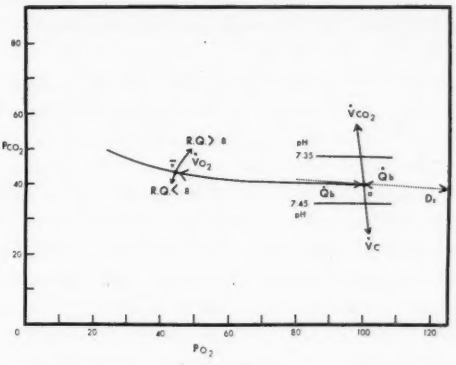

Fig. 16.

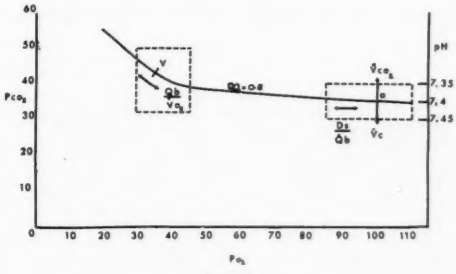

Fig. 17.

The perfusionist need only fix the venous point with respect to the oxygen tension. If the device with which the perfusionist is monitoring the $P\bar{v}_{O_2}$ is accurate within ±20 per cent, the pump flow rate can be adjusted so that the apparent $P\bar{v}_{O_2}$ is 40 mm. Hg and the true $P\bar{v}_{O_2}$ will lie well within the normal range for this parameter. If the oxygen consumption of the patient is higher than anticipated the venous point will move to the left along the RB line. To compensate for this effect the perfusionist must increase the blood flow rate from the pump. Conversely, if the perfusion rate is too high the venous point will move to the right along the RB line, and the rate of perfusion should be decreased.

To illustrate more fully how this system is linked together it might be of value to relate what might happen in a hypothetical case. Let us assume that we have estimated the oxygen consumption of the individual to be perfused, from some body weight-height nomogram. From this information and Fig. 9 one can estimate the rate of blood flow that might be required for this patient. If hypothermia is used, a lower value would obtain. From this data one could

also, by assuming an R.Q. of 0.8, estimate the rate of CO_2 production that such an individual might have. From this estimated rate of CO_2 production and knowledge that a gas flow rate to CO_2 production rate ratio of 0.05 is desirable, one could calculate what rate of flow of gas might be required for this patient in order to maintain a normal arterial pH. From empirical data relating the rate of blood flow to disc speed that is appropriate to give an oxygenating efficiency of 0.18, the perfusionist would then have an estimate of the disc speed that might be required by this patient. Let us assume that the perfusionist begins to perfuse the patient with these first estimates, and he finds that the $P\bar{v}_{O_2}$ is 30 mm. Hg. This means that he has underestimated the rate of oxygen consumption of the individual and he must increase the rate of blood flow to the patient. As he increases the rate of blood flow to the patient to bring the venous point to a higher P_{O_2} level, this causes the arterial point to move to the left. The Pa_{O_2} will decrease because the equilibrating efficiency will have decreased by the increase in blood flow to the patient. This fact then demands that the perfusionist increase the disc speed so that the apparent Pa_{O_2} is 100 mm. Hg. Since the initial estimate of the rate of oxygen consumption of the patient was low, it is probable that the estimate of the rate of CO_2 production was also low. If this is true, then the arterial point would initially move up on the graph as it moved to the left. The perfusionist then would increase the rate of oxygen flow through the oxygenator to return the pH to 7.40.

SUMMARY

The cardiorespiratory characteristics of artificial pump-oxygenating systems have been theoretically analyzed by the use of graphical analysis. To make this analysis as simple as possible, several simplifying assumptions were made. This analysis described several combinations of monitoring systems that might be used to give the patient an adequate perfusion without exact knowledge of either the rate of oxygen consumption of the patient or of the perfusion rate. One of these possible systems was described in some detail for use with a rotating disc oxygenator. This system is in current use at the University of Colorado Medical Center. How close real perfusions come to the ideals described in the present paper will be the subject of a future report.

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PULMONARY VENTILATION IN HYPOTHERMIA

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Private First Class, Denver, Colo.

As compared with investigation of cardiovascular changes during hypothermia, relatively little work has been done on the ventilatory system. Breathing is generally described in terms of two components: (1) ventilation and (2) respiration.[1] Ventilation constitutes the mass movement of air in and out of the lungs and the distribution of air within the alveoli. This activity is achieved through the mechanical parts of the breathing apparatus, measurements of which include lung volumes, maximum breathing capacity, minute ventilation, and intrapulmonary gas distribution. Respiration is the physicochemical phase which involves the transport of gases by the blood and their exchange across the alveolocapillary membrane. To the latter, a fundamental component is the pulmonary capillary blood flow.

Studies on respiration changes in hypothermia have demonstrated a respiratory acidosis.[2, 5, 9] Diffusion of gases across the alveolocapillary membrane is apparently not adversely affected.[6] Oxygen consumption decreases linearly with falling temperature.[8] Severinghaus and Stupfel[7] found that the compliance was somewhat decreased and the dead space increased. Death from hypothermia is generally attributed to respiratory failure followed by circulatory failure.[5]

The retention of CO^2, as evidenced by the respiratory acidosis in hypothermia, may be due to deficient ventilation. The present study is an evaluation of the effect of hypothermia upon some aspects of the mechanical component of ventilation as assessed by minute ventilation, helium excretion as an index of intrapulmonary gas distribution, and the functional residual capacity (FRC).

METHOD AND MATERIAL

Study was carried out on dogs under chloralose anesthesia and with unassisted ventilation. Despite the fact that, in heavy doses, chloralose can produce central respiratory depression, respiratory reflex excitability under this agent is increased.[3] Following the achievement of a relative "steady state," as determined by rate and depth of respiration, the functional residual capacity and rate of excretion were determined by the open-circuit helium method.[4]

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Essentially, in this method, the animal breathes a 50-50 mixture of helium and oxygen for a period of 10 minutes to allow for equilibration of the gas in the alveoli. At the end of a normal expiration, the animal is switched to tank oxygen and the helium is washed out. The helium is passed through a system for continuous analysis by a sensitive katharometer.* The rate of excretion of of helium serves as a general index of the gas mixing. The gas is collected in a Douglas bag from which the minute ventilation and the functional residual capacity is calculated. All gases have been corrected to STPD (standard temperature pressure dry).

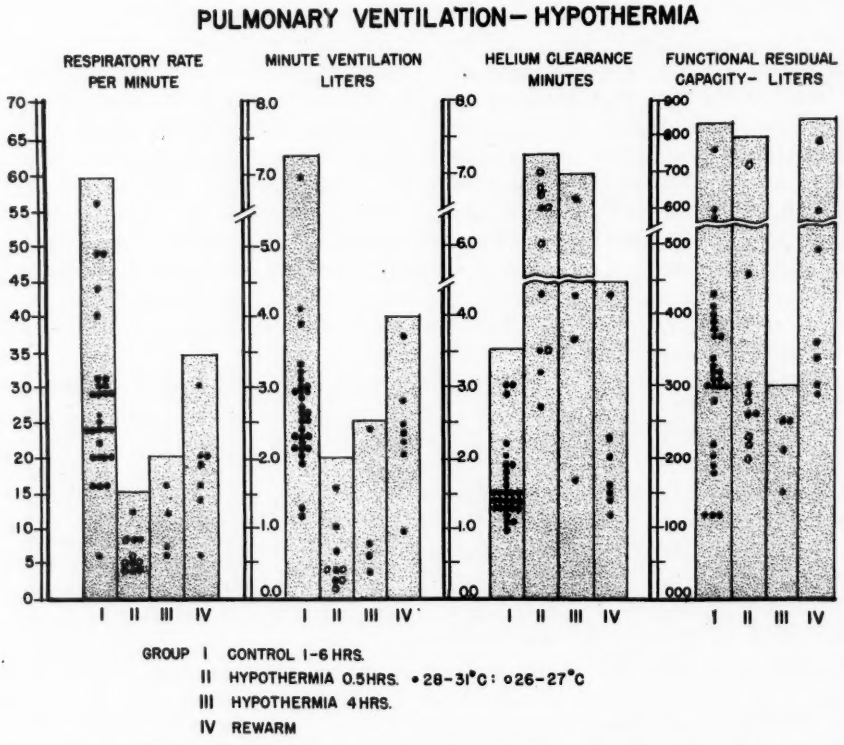
PULMONARY VENTILATION— HYPOTHERMIA
RESPIRATORY RATE PER MINUTE
MINUTE VENTILATION LITERS
HELIUM CLEARANCE MINUTES
FUNCTIONAL RESIDUAL CAPACITY— LITERS
I II III IV
GROUP I CONTROL 1-6 HRS.
II HYPOTHERMIA 0.5 HRS. • 28-31°C : o 26-27°C
III HYPOTHERMIA 4 HRS.
IV REWARM

Fig. 1.—Significant depression in pulmonary ventilation occurs only below 28° C. In prolonged hypothermia (4 hours) there is improvement in over-all ventilation. Upon rewarming ventilation returns toward normal.

Animals in the study were divided into the following groups: *Group A*—Control. Six animals under chloralose anesthesia with analyses at 1, 3, and 6 hours of anesthesia to determine the effects of this agent over a prolonged period of time. *Group B*—Seven animals subjected to hypothermia ranging from 31° to 27° C., and then rewarmed. *Group C*—Four animals cooled to levels of 27° to 26° C. and maintained for 4 hours at this temperature.

*Gow-Mac Instrument Co., Madison, New Jersey.

TABLE I. PULMONARY VENTILATION—NORMOTHERMIA CONTROLS
AVERAGE OF 6 DOGS—CHLORALOSE ANESTHESIA

TIME (HOURS)	RATE PER MIN.	MINUTE VENTILATION (L./MIN.)	TIDAL VOLUME (ML.)	HELIUM CLEARANCE (MIN.)	FUNCTIONAL RESIDUAL CAPACITY (ML.)
1	29	2.44	110	1.8	310
3	30	2.90	95	1.5	440
6	32	3.70	110	1.5	370

RESULTS

Group A.—Controls. The averages of the 6 animals are compiled in Table I. Over a period of 6 hours there was no significant change in the respiratory rate. Seventy per cent of the animals had a rate between 20 and 30 per minute, as shown in Fig. 1. The minute ventilation increased during the latter part of the study. For the entire group, 83 per cent of the animals had a minute ventilation between 2 and 3 L. The tidal volume remained essentially unchanged, and averaged 100 ml. The clearance of helium was essentially unchanged, and, in 90 per cent of the animals, this time varied from 1 to 2 minutes with an over-all average of 1.5 minutes. The functional residual capacity was quite variable in this group, with 59 per cent having an FRC of 300 to 400 ml. Except for a significant increase in the minute ventilation and a minimal increase in the FRC, there were no gross changes in ventilation during the 6-hour period of control anesthesia observation.

TABLE II. GROUP B. HYPOTHERMIA AND REWARM—CHLORALOSE ANESTHESIA

NO.	TEMPERATURE (°C.)	RATE PER MIN.	MINUTE VENTILATION (L./MIN.)	TIDAL VOLUME (ML.)	HELIUM CLEARANCE (MIN.)	FUNCTIONAL RESIDUAL CAPACITY (ML.)
1.	39.2	20	2.89	145	1.9	395
	31.0	12	1.56	130	2.7	455
	39.2*	16	2.33	145	2.3	490
2.	38.6	16	1.21	76	3.0	310
	31.0	8	1.00	125	3.2	300
	39.3*	30	2.22	74	1.4	300
3.	38.0	24	2.63	109	2.0	200
	30.0	8	0.66	82	3.5	260
	37.4*	14	3.69	265	1.2	290
4.	39.2	20	2.58	130	1.5	330
	28.1	4	0.25	63	6.5	260
	39.2*	20	2.79	140	1.5	780
5.	38.2	24	2.25	94	1.5	119
	27.8	5	0.38	77	4.3	290
	38.5*	18	2.05	115	2.0	590
6.	39.2	20	2.10	105	1.5	370
	27.2	4	0.24	60	6.0	220
	39.2*	20	2.35	120	1.6	340
7.	37.5	16	2.47	155	1.5	120
	27.2	4	0.36	90	6.5	280
	37.5*	6	0.96	160	4.3	360

*Rewarm.

Group B.—Data referable to the animals cooled and then rewarmed appear in Table II. There was significant reduction both in the respiratory rate and in the minute ventilation at all levels of hypothermia studied (31°-27°). However, marked prolongation of time required for helium clearance occurred only at 28° C. and below. Generally, the deeper the hypothermia, the greater the decrease in minute ventilation and the greater the increase in time required for helium clearance. The FRC during hypothermia did not show any significant alteration for the hypothermic group as a whole. Upon rewarming, the respiratory rate returned toward normal. The minute ventilation increased and, in the majority of animals, fell within the normal range. The helium clearance time returned to essentially normal limits. The FRC remained somewhat high in less than half the animals rewarmed.

Group C.—Following 4 hours of hypothermia, the animals demonstrated improvement in their ventilation. The respiratory rate increased somewhat as shown in Table III. The minute ventilation and tidal volume improved, and the time required for helium clearance in 3 of the 4 animals was reduced. The FRC also became somewhat reduced as compared to the short-term hypothermic group (Fig. 1).

TABLE III. GROUP C. PROLONGED HYPOTHERMIA (4 HOURS) AND CHLORALOSE

NO.	TEMPERATURE (°C.)	RESPIRATORY RATE PER MIN.	MINUTE VENTILATION (L./MIN.)	TIDAL VOLUME (ML.)	HELIUM CLEARANCE (MIN.)	FUNCTIONAL RESIDUAL CAPACITY (ML.)
1.	37.3	48	2.94	61	1.1	120
	26.2	8	0.40	50	3.5	230
	26.5*	16	2.42	150	1.7	210
2.	37.6	16	2.41	150	1.1	280
	26.0	4	0.19	48	6.8	200
	27.0*	7	0.57	80	3.7	250
3.	37.9	24	2.00	83	2.8	340
	27.0	5	—	18	—	720
	27.0*	6	0.36	60	6.7	250
4.	38.2	22	2.14	97	1.3	310
	27.4	5	—	—	8.7	—
	26.4*	12	0.73	61	4.3	150

*Hypothermia – 4 hours.

DISCUSSION

Hypothermia results in a marked reduction in pulmonary ventilation, as evidenced by reduced respiratory rate and minute ventilation. This has been observed by other investigators.[2, 8] Helium clearance which provides a general index of intrapulmonary gas mixing was prolonged suggesting impairment of ventilation. The depressed ventilation appears to be essentially a function of the reduced temperature. As shown in Fig. 2 there is a linear relationship between the respiratory rate and the minute ventilation. As the rate becomes significantly reduced, the minute ventilation concomitantly becomes smaller. If mechanical components concerned with ventilation were unaltered by hypothermia, it might be anticipated that, despite the reduced rate, the volume of air

moved in and out of the lungs might be fairly considerable; however, in these studies this is apparently not the case, suggesting some impairment in the mechanics of breathing. The defective alveolar ventilation during hypothermia is demonstrated in Fig. 3. There is, in general, a parabolic relationship between minute ventilation and the excretion of helium. Below a ventilation rate of 1 L. per minute, the time required for excretion of helium may vary from 3 to 7 minutes. Of significance, however, is the fact that this activity returns to normal upon rewarming. A ratio between minute ventilation (MV) and the

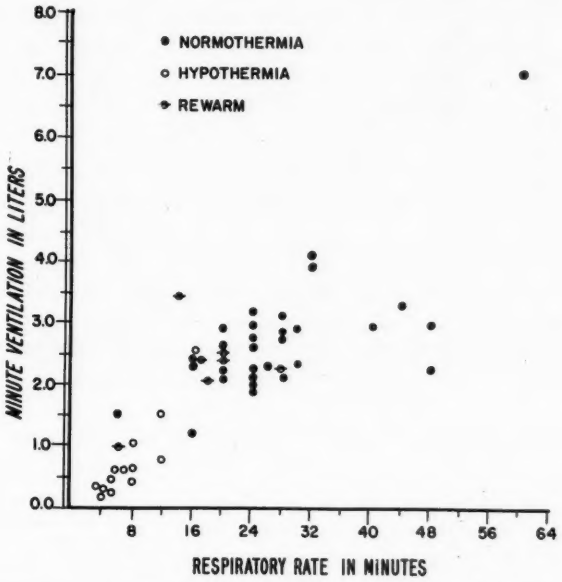

Fig. 2.—A generally linear relationship between respiratory rate and minute ventilation is demonstrated. The relationship is retained during hypothermia, suggesting mechanical as well as central and/or reflex depression.

helium excretion time (He_t), termed the ventilation efficiency ratio (VER), was developed to illustrate the changes of efficiency of ventilation during hypothermia. A VER not exceeding 0.4 is considered to be within normal limits. As demonstrated in Fig. 4, the efficiency becomes very markedly reduced at hypothermic levels of 28° C. and below with, however, significant improvement in ventilatory efficiency at the end of 4 hours of cold exposure. The improvement of ventilation during prolonged hypothermia is doubtless due to an improvement in over-all ventilation. This might well be due to a response of the respiratory center to the pCO_2 stimulus since, during hypothermia, the pCO_2 becomes elevated.[1] While there is a possibility that the reflex responses to CO_2 may be depressed, it appears likely from this study that, while thresholds to stimuli may alter somewhat, elevated pCO_2 may still elicit an adequate response from peripheral respiratory reflexes in prolonged hypothermia.

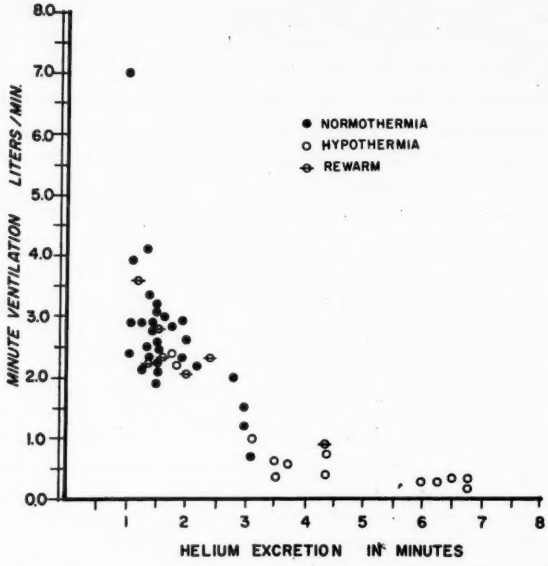

Fig. 3.—Depression of the minute ventilation during hypothermia is accompanied by increased defective intrapulmonary gas mixing, as indicated by prolonged excretion time of the helium. The degree of defective gas distribution varies greatly. These functions return to normal on rewarming.

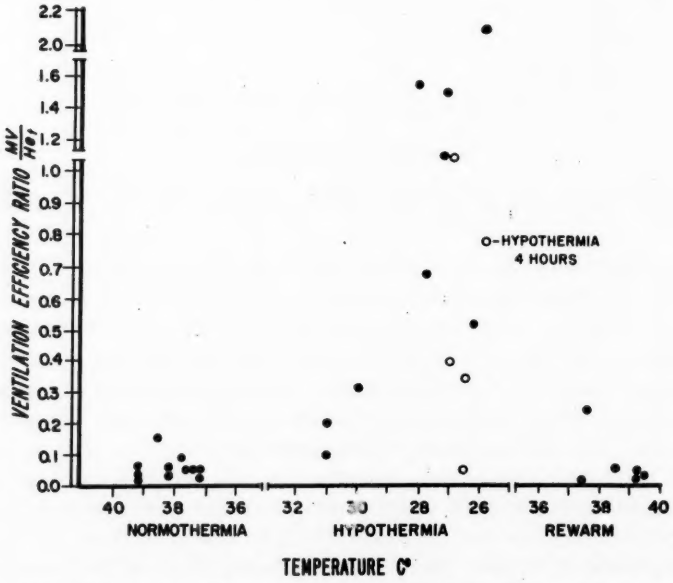

Fig. 4.—The efficiency of ventilation is seriously reduced at 28° C. and below, with improvement during prolonged hypothermia and return to normal on rewarming.

As a result of the marked ventilatory depression at 28° C. and lower, significant unsaturation and CO_2 retention would likely occur.

The precise involvement of the various mechanical components during hypothermia is not known. It has been demonstrated that there is some increase in dead space and some decrease in compliance.[6] These changes, along with the possible increased resistance to breathing, would indicate increased work required for breathing. Alterations in these mechanical factors, together with central depression due to cold narcosis, could well account for the reduced efficiency of ventilation as demonstrated in these studies. The changes, however, appeared to be transient, and, upon rewarming, ventilatory activity returned to normal limits.

CONCLUSIONS

Study of pulmonary ventilation was carried out in dogs under chloralose anesthesia under hypothermia and upon rewarming. The level of hypothermia varied from 31° to 26° C.

There was a marked depression in pulmonary ventilation at 28° C. and below, which improved somewhat under prolonged hypothermia. The depression is likely central in origin, although some alteration in the mechanics of breathing may also occur. The improvement after 4 hours of hypothermia is probably due to return of an adequate threshold response of the respiratory reflexes to pCO_2.

Upon rewarming, the pulmonary ventilatory functions measured returned toward normal limits.

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ACIDOSIS FOLLOWING RESPIRATORY ALKALOSIS IN THORACIC OPERATIONS WITH AND WITHOUT HEART-LUNG BYPASS

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IN THE PAST DECADE anesthetists have become aware of the likelihood and the danger of carbon dioxide retention during anesthesia.[3, 8] The reaction to this knowledge has been a tendency to hyperventilate the patient. With respiration thus assisted by the anesthetist, depression of the arterial carbon dioxide tension may occur, particularly with the use of a muscle relaxant and complete control of ventilation by the anesthetist. This is particularly true in children. The observations reported herein concern the blood changes that occur after respiratory alkalosis produced by prolonged hyperventilation during thoracic operations.

MATERIAL

The patients considered in this report fall into two groups—the "pump-oxygenator" group and the "control" group. The former consisted of 22 consecutive patients undergoing open heart surgery for a variety of congenital cardiac lesions using a screen-oxygenator.* There were two adults, aged 41 years and 58 years, in this group; the remainder were children weighing for the most part between 10 and 20 kilograms. Three patients died postoperatively. Two of these had had tetralogy of Fallot and the other had had a functional single ventricle with pulmonary hypertension. An anatomic cause of death was present in each case.

The control group consisted of 8 children undergoing other thoracic operations. Five had ligation of a patent ductus arteriosus, 2 had lobectomies, and 1 division of a vascular ring.

METHODS

The determinations under consideration include the arterial carbon dioxide tension (pCO_2), the whole blood pH, and the plasma bicarbonate. Measurements were made with the Astrup apparatus.[1, 2]

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The blood in all cases was warmed to 38° C., and the observations are reported for the blood at that temperature regardless of the actual blood temperature at the time of sampling. Arterial samples were drawn under anaerobic conditions from a catheter in the radial artery. In the pump-oxygenator group, samples were drawn at the following times: (1) chest open before bypass, (2) late bypass, (3) chest open after bypass, and (4) after chest closure with spontaneous ventilation. In the control group, samples were drawn (1) before thoracotomy, (2) after opening the chest, (3) before closing the chest, and (4) after chest closure with spontaneous ventilation.

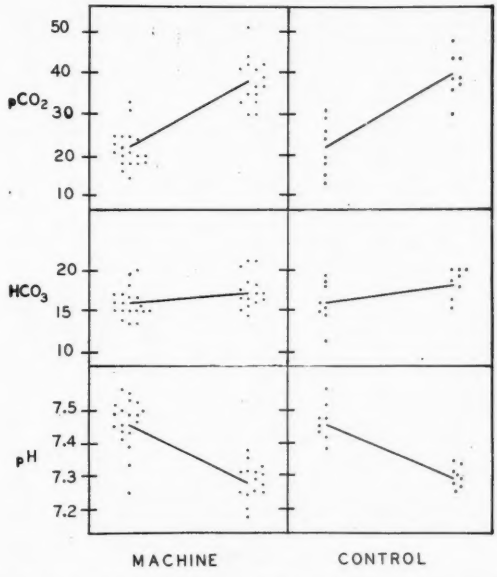

Fig. 1.—Arterial blood changes following prolonged respiratory alkalosis comparing the "heart lung bypass" and the "control" patients. In each half of the chart the values to the *left* represent conditions just prior to chest closure with manual ventilation by the anesthetist; the values to the *right* indicate the situation after chest closure with spontaneous ventilation. The pCO_2 has returned to normal in each group and the pH has fallen.

Anesthesia was similar for both groups of patients. They were premedicated with pentobarbital (1.5 mg./Kg.) 1½ hr. preoperatively, and morphine (0.1 mg./Kg.) and scopolamine (0.01 mg./Kg.) 1 hr. preoperatively. After induction, endotracheal anesthesia was maintained with 50 per cent nitrous oxide and oxygen. The patients were paralyzed with a muscle relaxant and were manually hyperventilated on a semi-open system with carbon dioxide absorption.

RESULTS

The results are listed in Tables I and II. The carbon dioxide tension was maintained at about 22 mm. Hg by the anesthetist until the patient was permitted to ventilate spontaneously. When spontaneous ventilation was resumed,

the average carbon dioxide tension rose from 22 to 38 and this was accompanied by a fall in pH from 7.46 to 7.29. A fall in pH always occurred. The late samples in Patient 57 have not been included in the average since there was inadequate relief of pulmonary outflow obstruction in this case of tetralogy of Fallot, and the patient had severe hypotension due to low output failure after the bypass.

TABLE I. PUMP-OXYGENATOR CASES

PATIENT NUMBER	CHEST OPEN BEFORE BYPASS			LATE BYPASS			CHEST OPEN AFTER BYPASS			AFTER CHEST CLOSURE SPONTANEOUS VENTILATION		
	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3
38	7.59	20	19.5				7.48	18	15	7.29	30	14.5
39	7.52	19	16.5				7.25	31	13.5			
40	7.50	35	26				7.48	21	16.5	7.24	42	17
41	7.42	27	18.5	7.24	50	18.5	7.33	33	17	7.20	41	15.5
42	7.54	21	18.5	7.45	25	17.5	7.43	25	16.5	7.26	51	21
43	7.56	23	21	7.44	22	15.5	7.50	20	15.5	7.32	35	17.5
44	7.40	25	15.5	7.40	19.5	13						
45	7.54	24	20.5	7.44	29	19.5	7.46	20	15.0	7.18	41.5	15.0
46				7.46	36	24.5	7.55	20	18	7.38	37	21
47				7.49	22.5	17.5	7.45	18	13			
48				7.48	22	17				7.30	42	20.5
49				7.38	29	17	7.42	22	15			
50	7.45	26	18	7.40	29	18	7.47	23	17	7.31	39	18.5
51	7.55	16.5	15.5	7.42	22	15	7.54	14.5	14	7.33	33	17
52	7.43	21.5	15	7.28	32.5	15	7.39	24.5	15	7.28	37	17
53	7.52	16	14	7.23	40	16	7.49	18	15	7.25	35	15
54	7.58	14	14.5				7.57	16	16	7.31	33	16
55	7.55	21	18.5	7.31	35	17	7.53	18	16	7.36	30	16.5
56	7.58	21	20	7.39	35	20.5	7.44	21	15	7.25	44	18
57	7.53	19	17	7.30	38	18	7.22*	36*	14.2*	7.23*	33*	13.5*
58	7.50	23	21.5	7.39	36	21	7.50	25	19.5			
59	7.57	22	20.5	7.31	48	22	7.52	24	20	7.40	43	25
Average	7.52	22	18.4	7.38	31.7	18	7.46	22	16	7.29	38	17.8

*Not included in average. Patient moribund.

TABLE II. CONTROLS

PATIENT NUMBER	AFTER ANESTHESIA CHEST CLOSED			CHEST OPEN			PRIOR TO CHEST CLOSURE			AFTER CHEST CLOSURE SPONTANEOUS VENTILATION		
	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3	pH	pCO_2	HCO_3
C-1	7.38	32	18.5	7.42	29	18.5	7.38	29	18.5	7.26	44	18.5
C-2	7.37	30	17	7.48	27	20	7.41	31.0	19	7.34	39	20
C-3	7.45	26	18.5	7.47	26	19	7.45	26	18	7.27	48	20
C-4							7.47	13.5	11.5	7.25	38	16
C-5	7.43	23	15.5	7.50	16	14	7.47	18	14	7.31	30	15
C-6							7.52	19.5	16.5	7.29	37	17
C-7	7.28	50.5	22	7.52	21	18	7.43	24	16	7.32	39	19
C-8	7.35	40	21	7.52	23	19	7.57	15	15	7.30	44	20
Average	7.38	34	19	7.49	24	18	7.46	22	16	7.29	40	18

In the control group similar observations were made. While the chest was open the average carbon dioxide tension was maintained at about 22 mm. Hg. After closure it rose to 40 mm. Hg, and this was accompanied by a fall in pH from 7.46 to 7.29.

A graphic comparison of the changes that occurred in the two groups on returning to spontaneous ventilation is shown in Fig. 1.

The fall in pH following respiratory alkalosis is further demonstrated in Fig. 2, in which the patient showing the greatest fall in pH is illustrated. This patient, who had an interventricular septal defect with severe pulmonary hypertension, had a satisfactory postoperative course. Fig. 3 illustrates the same type of change in 1 of the control cases.

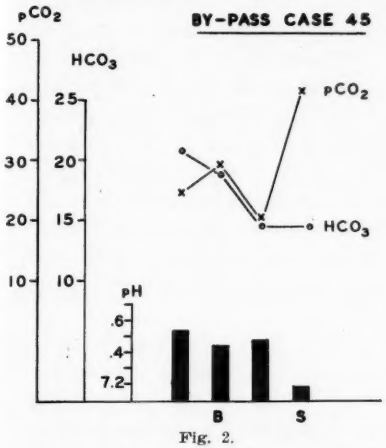

Fig. 2.

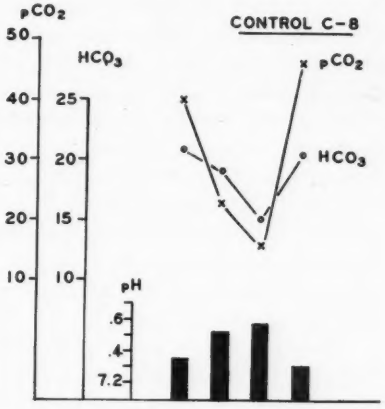

Fig. 3.

Fig. 2.—Biochemical changes following respiratory alkalosis in a patient undergoing ventricular septal defect repair. The solid bars from *left to right* represent pH values after opening the chest, during bypass (*B*), prior to chest closure, and after chest closure with spontaneous ventilation (*S*). The pH dropped from 7.46 to 7.18 following return of pCO_2 to a normal level.

Fig. 3.—Biochemical changes following respiratory alkalosis in a patient undergoing ligation of a patent ductus arteriosus. The solid bars from *left to right* indicate the arterial pH before thoracotomy, after opening the chest, prior to chest closure, and after chest closure with spontaneous ventilation. When hyperventilation was discontinued, the pCO_2 rose from 15 to 44 mm. Hg, and the pH fell from 7.57 to 7.30.

DISCUSSION

The acidosis that we have observed at the end of these operations is related to the low bicarbonate values; the carbon dioxide tension has rapidly returned to a normal level but the bicarbonate has remained depressed, forcing a drop in pH. Respiratory alkalosis reduces the bicarbonate concentration partly because a portion of the carbon dioxide in the blood is present as bicarbonate,[6] and partly for reasons discussed below. The respiratory alkalosis may be assumed to be in large part responsible for the lowered bicarbonate values seen in the course of these operations in both groups of patients. As the operations proceeded, the bicarbonate dropped further. In the pump-oxygenator patients, it dropped from 18.7 mEq. per liter after the chest was opened to 16 before chest closure; the carbon dioxide tension was 22 mm. Hg in each sample. In the control patients, the corresponding drop was from 18 mEq. per liter to 16 without significant change in the pCO_2. This continuing depression in bicarbonate could be a compensation for the prolonged alkalosis by renal excretion of bicarbonate, or fixed acids may have accumulated. Experimentally the rate

of reabsorption of bicarbonate by the renal tubules is a direct and linear function of the carbon dioxide tension.[5] As the pCO_2 falls, so does the bicarbonate reabsorption and the plasma bicarbonate concentration is thereby reduced.

Fixed acid accumulation can also result from respiratory alkalosis. Boucot and associates[4] recorded the glycolytic response to vigorous hyperventilation with increase in lactate ion. Ionic shifts in respiratory alkalosis have been studied by Elkinton,[7] who showed that an anion shifted out of the cells, which, on the evidence of Giebisch,[9] was felt to be lactate. More recently Huckabee[11] showed an increase in lactate on hyperventilation, whether active in man or passive in paralyzed animals on a ventilator. He pointed out that rapid lactic acid accumulation during hyperventilation represents a mechanism for quickly reducing body bicarbonate as an adjustment to alkalosis. Others[10] have demonstrated the same rise in anesthetized hyperventilated patients. Litwin and associates[12] pointed out the biochemical similarities between hypoxic acidosis and respiratory alkalosis, particularly the increase in lactate and chloride and the decrease in bicarbonate and potassium. The bicarbonate depression during these operations could also be due to fixed acid accumulation produced by factors other than respiratory alkalosis, notably tissue hypoxia either during normal or extracorporeal circulation.

Malette[13] has demonstrated cerebral tissue anoxia from hyperventilation in dogs. Although cerebral vasoconstriction played a part, hypoxia was mainly due to resistance of alkaline hemoglobin to release bound oxygen. The venous oxygen was therefore high despite tissue anoxia. The alkalosis in these animals was much more severe than in the patients reported herein. Should this mechanism apply at levels of alkalosis observed clinically, then venous oxygen saturation could not be taken as an indication of the adequacy of tissue oxygenation.

There seems no necessity to implicate the pump-oxygenator, however, as similar changes were seen in the control group. The bypasses in these cases were carried out with an average flow rate of 98 c.c. per kilogram per minute, and the venous oxygen saturation averaged 72 per cent, the lowest being 54 per cent. The flow rate was, therefore, adequate, and acidosis on the basis of inadequate tissue perfusion would not be expected.

All but 2 of the patients studied in this report were children. That the changes reported herein are less likely to occur in adults is a distinct possibility. We have noticed a tendency for the bicarbonate level to remain higher in adults and, therefore, the pH shift on re-accumulating carbon dioxide at the conclusion of the operation has been less profound.

Although the level of acidosis observed in these cases is mild in most instances, it is the sudden drop in pH that has concerned us. We have not observed any clinical ill effects during this period of transition from controlled to spontaneous ventilation.

SUMMARY

In a series of thoracic operations carried out with hyperventilation, the carbon dioxide tension was reduced to 22 mm. Hg. When carbon dioxide

reaccumulation was permitted at the end of operation, a sudden fall in pH occurred. The findings were similar in two groups of patients, one undergoing extracorporeal circulation for intracardiac surgery and the other having had other thoracic procedures. All but 2 of the patients were children.

The technical assistance of Miss B. Thomas and Mr. W. Schroeder is gratefully acknowledged.

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RAPID HYPOTHERMIA: AN IMPROVED EXTRACORPOREAL METHOD

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HYPOTHERMIA has been successfully employed in various forms as an adjunct to cardiac surgery—in the past by surface contact techniques,[1, 2] and more recently via the extracorporeal circulation.[3-10] The combination of hypothermia with extracorporeal circulation reduces metabolic requirements and blood flow rates, increases the efficiency of oxygenation, and enables longer safe perfusions. It allows the perfusion of large patients whose flow rate would otherwise exceed the capacity of a given oxygenator at normothermia.

Since the efficiency of both blood oxygenation and heat transfer depend on a maximum exchange surface per unit blood flow, an apparatus was developed to combine these functions within the oxygenator. This unit, which adapts to the rotating disc oxygenator, consists of a series of semicircular, stainless steel coils connected in parallel. An electronically controlled unit circulates water at the desired temperature through the coil thereby providing rapid, safe, and precise control of blood temperature.

This method of rapid hypothermia and rewarming is accomplished with total cardiopulmonary bypass and incorporates all of the prerequisites for ideal thermal regulation: (1) maximum efficiency of heat exchange, (2) precise and simple control of blood temperature, (3) safety with regard to the production of gas emboli developed during rapid rewarming, (4) no impedance to blood flow, (5) minimal injury to blood elements, and (6) no additional priming volume.

Extracorporeal hypothermia as utilized clinically today is initiated via the femoral vessels with partial bypass prior to thoracotomy. In contrast, this method effects heat exchange on total cardiopulmonary bypass without prolongation of operative time or commitment to hypothermia before the intrathoracic situation has been evaluated.

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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EXPERIMENTAL DESIGN

To evaluate this method of thermoregulation and to study the effects of rapid total body cooling and rewarming, a series of experiments was designed. The following factors were examined: (1) the efficiency and rate of blood and body temperature change, and (2) the safety of rapid thermal alterations with regard to (a) the temperature gradient which can be applied to the blood without producing damage, (b) the effect of this apparatus on blood elements and oxygenation, (c) the formation of bubble emboli upon rapid rewarming, and (d) the blood electrolyte and pH change.

Following evaluation, this thermoregulation unit was incorporated into the extracorporeal circuit for the production of rapid hypothermia and rewarming as well as maintenance of normal temperature in human perfusions.

APPARATUS

The apparatus for extracorporeal blood thermoregulation consists of two parts: (1) a coil (Fig. 1) that conducts water and adapts to the inside of the Kay-Cross rotating disc oxygenator,[11] and (2) an electronically controlled pumping unit (Fig. 2) containing hot and cold reservoirs.

The coil is a series of ⅛ inch diameter stainless steel tubing semicircularly molded, and connected in parallel. The longitudinal inflow and outflow conduits perforate the end plates near the top and are connected to the thermoregulation pumps, reservoirs, and electronic control unit. The glass reservoir is ½ inch larger in diameter than the standard size in order to accommodate the coil and maintain the same priming volume. Coils of different lengths adapt to the 13-, 17-, and 21-inch oxygenators.

The pumping unit consists of two water reservoirs, and two centrifugal pumps which circulate fluid through the coil at a rate of 6 gallons per minute. The warming reservoir is equipped with a thermostatically controlled 2,000 watt heater and provides rapid attainment of temperatures between 0° to 60° C. The warming fluid may be internally recirculated to maintain a given temperature, or pumped through the coil. The cooling reservoir is held constant at 1° to 3° C. with ice water which is always available for coil circulation. Interlocking solenoid valves enable instantaneous shift from one reservoir output to the other, providing maximum temperature gradients for blood thermoregulation.

METHODS

Animal Investigation.—Mongrel dogs varying in weight from 11 to 22 Kg. were anesthetized with intravenous Nembutal, intubated, and mechanically respirated with 97 per cent oxygen and 3 per cent carbon dioxide. Cannulations of the right femoral artery for input of oxygenated blood and of the venae cavae, via the right atrium, for venous drainage were performed.

The oxygenator containing the thermoregulatory coil was primed with heparinized blood, drawn the previous day. A calibrated variable stroke volume

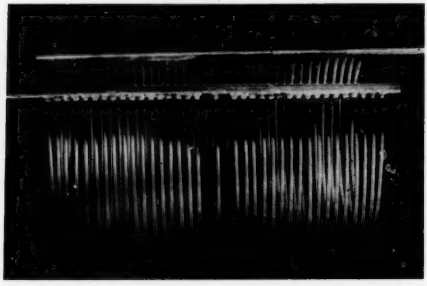

Fig. 1.—Heat exchange coil.

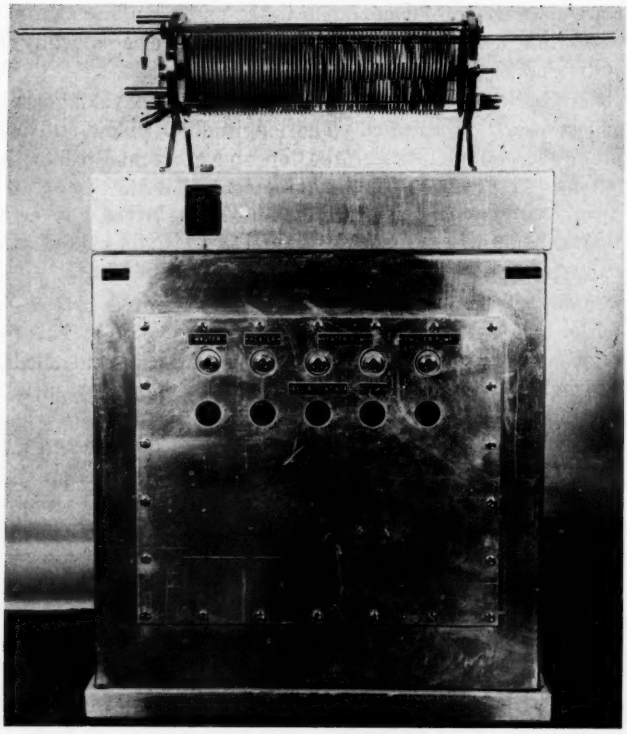

Fig. 2.—Thermoregulation unit and assembled oxygenator.

and stroke rate piston-type pump with occlusive flap valves at each end of a Tygon chamber was employed. Cardiopulmonary bypass was established using gravity drainage into the oxygenator.

Animal perfusions were separated into two groups of 12 and 11 animals each. In the first group, esophageal temperature was lowered to 28° C. and in the second group to levels from 10° to 22° C.* After stabilization of pressures at a perfusion temperature of 37° C., rapid cooling was initiated with 1° to 3° C. water in the cooling circuit. When the desired level of hypothermia was achieved, the blood temperature was controlled to maintain the esophagus at that level for ½ hour. A right ventriculotomy was performed and repaired during this period. Coronary blood from the open cardiotomy was returned via a roller pump to the oxygenator. Rapid rewarming of the blood and body was then effected by circulating water at 44° C. through the coil.

Thermocouples recording on a Brown potentiometer were placed in the mid-esophagus, rectum, thigh muscle, right ventricle, as well as the venous and arterial ends of the oxygenator. Inflow and outflow coil temperatures were

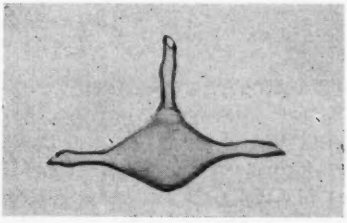

Fig. 3.—Plenum chamber.

constantly recorded. Blood oxygenation was monitored with a Clark oxygen electrode inserted in the arterial end plate. Venous and arterial pressures were monitored via left femoral vessel cannulae.

A plenum chamber (Fig. 3) was inserted into the arterial end of the oxygenator in parallel with the outflow tract to discern any microbubbles evolved during rapid rewarming. This device provides a decrease in linear flow by virtue of increased cross sectional area, thus permitting bubbles to rise and be trapped in the top of the chamber.

Blood samples were obtained at intervals of 5 to 10 minutes from the patient and oxygenator for determination of platelets, white blood cells, plasma hemoglobin, pH, and serum Na^+, K^+ and Ca^{++}. A control aliquot was maintained at 37° C. and sampled simultaneously with the oxygenator blood samples.

To determine safe parameters for heating and cooling blood, in vitro experiments were performed on freshly drawn dog blood drawn the day of the procedure. Using siliconized equipment and exercising maximum care in blood handling, the extracorporeal circuit was primed as in the animal experiment, substituting a reservoir for the dog. A control blood sample was maintained in a 37° C. water bath.

*Cardioplegia was produced and maintained with hypothermia at temperature levels below 20° C. Results of this investigation will be reported elsewhere.

TABLE I. THERMOREGULATION DATA FROM ANIMAL EXPERIMENTS

DOG	WEIGHT (KG.)	FLOW COOLING (C.C./KG.)	ESOPHAGUS RATE COOLING (°/MIN.)	MIN. ESOPHAGUS TEMP. (°C.)	MIN. BLOOD TEMP. (°C.)	RATE BLOOD COOLING (°/MIN.)	FLOW WARMING (C.C./KG.)	ESOPHAGUS RATE WARMING (°/MIN.)	RATE BLOOD WARMING (°/MIN.)
24	22.2	54	0.70	28	18	13	50	0.21	1.6
25	22	55	1.38	25	14	11	55	0.27	1.8
37	16	75	2.00	28.5	10	9	60	0.90	1.2
38	11	68	1.00	29.4	9	11	54	0.47	4
40	18	77	2.00	28.6	20	16	55	0.63	5
41	20	100	1.50	26.8	19	10	60	0.65	1.4
42	14.5	90	1.30	28	16	11	65	0.50	2
43	11	90	2.30	29.5	16	12	90	1.0	6
57	16	63	0.90	31.5	13	14	63	0.33	5
60	14	21	0.70	26.5	8	15	43	0.33	6
61	18	67	1.0	25.5	16	11	83	1.0	7
62	16	44	1.0	27	13	10	44	0.47	4
26	18	78	2.30	22	12	10	78	0.75	2.5
27	13	45	0.95	21	5	11	45	0.33	2.6
28	13	38	0.65	21	5	16	23	0.24	4.3
29	13	50	1.30	11.6	3	7	38	1.0	9
30	20	55	1.16	22.8	13	7	60	0.6	3
31	13	46	1.00	24	9	6.5	69	0.55	2.5
32	13	77	1.10	24.6	8	13	38	0.55	6
59	18	120	1.75	16	15	11	93	0.88	5
63	14	29	1.0	22.5	12	7	43	0.63	5
64	13.5	45	2.0	15.5	14	16	45	0.83	8
65	23.6	85	2.9	11.5	6	11	55	0.90	8

For determination of the critical upper thermal limit, blood was circulated at 37° C. and then raised 1° every 5 minutes to a temperature of 50° C. At the end of each 5-minute period, a sample was taken from the oxygenator and the control for the determination of plasma hemoglobin, white blood cells, and platelets. Varying temperatures of coil fluid were utilized to establish safe limits for blood contact. When the temperature at which the blood began to exhibit damage had been determined, fresh blood was placed in the bypass circuit. It was circulated for 20 minutes at each degree of temperature beginning 3° below and increasing through the thermal level producing damage. In this way the safe upper limit of blood temperature in the extracorporeal circuit was determined as well as the optimum water temperature gradient which could safely be applied to the coil.

To investigate the lower thermal limit, blood at 37° C. was exposed to a coil temperature of 1.5° C. with the animal in the circuit. The blood rapidly dropped to 4° C. where it was maintained for one half hour. Since blood elements were not damaged in excess of control values it was unnecessary to continue these experiments in vitro.

RESULTS

Experimental Results.—Twenty-three mongrel dogs were subjected to rapid body cooling and rewarming. Blood flow rates were different from animal to animal and varied with temperature (Table I). Maximum rates of cooling were 16° C. per minute for blood and 2.9° C. per minute for the esophagus. The velocity of rewarming was slightly less than that of cooling with a maximum blood rate of 9° C. per minute and an esophageal rate of 1.0° C. per minute. Once the desired temperature level was reached it was possible to control it within ±0.5° C.*

The rates of cooling and rewarming were directly proportional to the rate of flow as is shown in Figs. 4 and 5. When the esophageal temperature was lowered the venous return to the oxygenator decreased. At 30° C., it was approximately 50 per cent of the flow at normothermia. Consequently, the more rapid changes of temperature occurred in the higher temperature ranges with regard to the flow effect. This factor operated independently of the gradient advantage available in the water bath, which enabled an increased rate of cooling, but a decreased rate of rewarming.

It was also observed that even with similar blood flow rates per unit of weight and identical blood temperature changes, different animals occasionally cooled at dissimilar rates. The viscosity of the blood increased with the decrease in temperature and blood flow.

Efficiency of this heat exchange unit can be calculated in the following manner:

$$\text{Efficiency} = \frac{\text{Blood temperature rise or fall}}{\text{Temperature of inlet blood} - \text{Temperature inlet } H_2O} \times 100.$$

*These limits of control were corroborated when the unit was employed for maintenance of normothermia in 60 animal and 10 clinical patients.

The efficiency of cooling and warming is approximately 70 per cent. However, the velocity of warming is lower because of the thermal gradient to which blood can safely be exposed. The efficiency varies slightly with the blood flow through the oxygenator (Fig. 6) but is not significantly affected by changes in disc rotation or rate of oxygen flow.

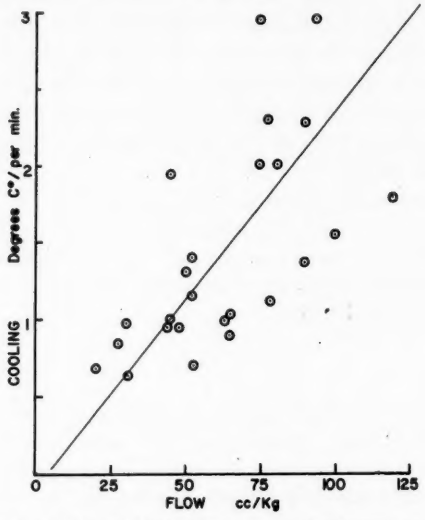

Fig. 4.—Effect of blood flow rate on esophageal cooling.

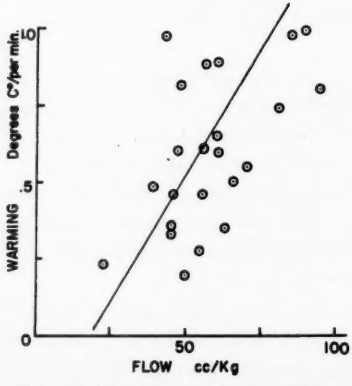

Fig. 5.—Effect of blood flow rate on esophageal warming.

Direct blood heat exchange provides for uniform rapid cooling and warming of the vital organs, the esophagus responding immediately and the heart following at a somewhat slower rate (Fig. 7). Both closely parallel the blood temperature change. The skeletal muscle of the thigh changes at a much slower rate and never attains the internal organ temperature within the duration of our experiments. The rectal temperature has been found to be

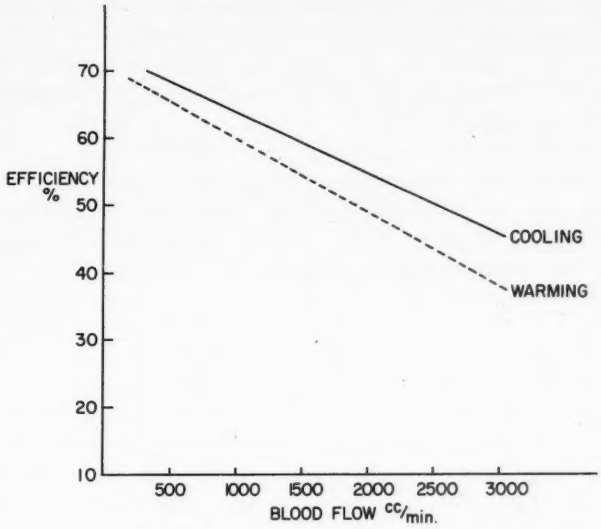

Fig. 6.—Efficiency of thermoregulation with varying blood flow rates.

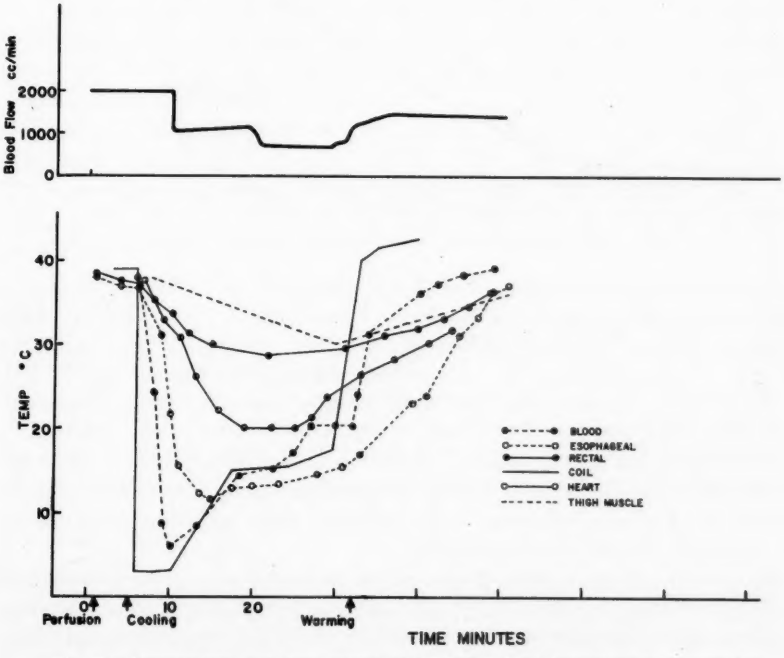

Fig. 7.—Temperature and flow record of typical animal hypothermia experiment.

the most variable in its rate of temperature change, with the final stabilized thermal level between that of the vital organs and the muscle.

Utilizing 1.5° C. water in the coil, a blood temperature of 4° C. was achieved consistently without any significant change in blood elements from the normothermic controls.

The in vitro investigation revealed the upper thermal limit to be a coil temperature of 45° C. which produced a blood temperature of 43.5° C. At coil temperatures above 45° C., considerable hemolysis and thrombocytopenia occurred. With coil temperatures of 43° to 45° C., circulation of blood for 20 minutes disclosed no increase of blood damage with increased time (Fig. 8).

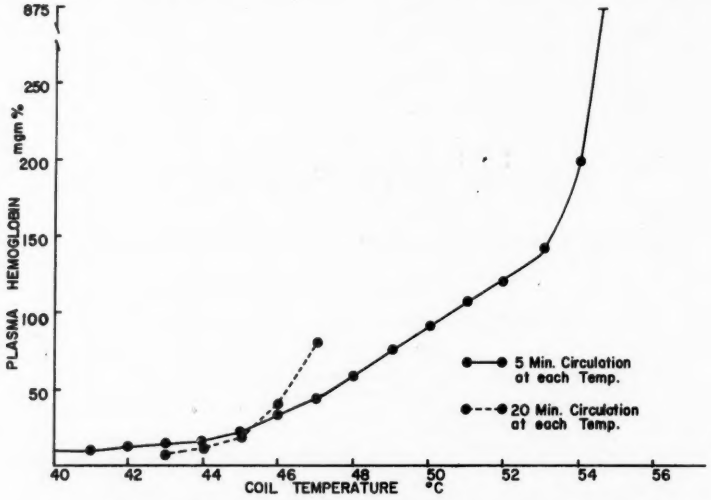

Fig. 8.—Effect of temperature on plasma hemoglobin production.

On the basis of these findings, coil temperatures of 44° C. were employed throughout our experiments as the upper thermal limit for rewarming with the maintenance of excellent blood element values (Table II). No significant difference was noted from the control normothermic perfusions (Table III) and therefore it is concluded that rapid cooling and rewarming within the limits established, are completely safe in regard to blood element damage.

The higher ranges of blood destruction occurred in cases with large coronary sinus suction return. Perfusion durations up to 180 minutes without coronary sinus blood suctioning were associated with an average increase of only 20 mg. per cent plasma hemoglobin.

Serum electrolyte determinations on the serial blood samples revealed no significant changes of Na^+, K^+, or Ca^{++} during hypothermia or rewarming. There was some depression of pH during hypothermia to levels from 7.18-7.28, but at the close of perfusion pH was always within normal limits.

The presence of the thermoregulatory coil within the oxygenator permitted the blood level to fall as low as 1½ inches below the recommended level

TABLE II. BLOOD ELEMENT DAMAGE DURING 60-MINUTE EXTRACORPOREAL CIRCULATION WITH RAPID COOLING AND REWARMING

	RANGE	AVERAGE
Plasma hemoglobin (increase)	5-90 mg.%	38 mg.%
Platelets (decrease)	50,000-250,000	110,000
WBC (decrease)	2,000- 5,000	2,600

TABLE III. BLOOD ELEMENT DAMAGE DURING 60-MINUTE NORMOTHERMIC EXTRACORPOREAL CIRCULATION

	RANGE	AVERAGE
Plasma hemoglobin (increase)	3-110 mg.%	41 mg.%
Platelets (decrease)	65,000-210,000	120,000
WBC (decrease)	1,900- 6,000	2,900

without foaming or frothing. Without the coil, marked foaming occurred with as little as ½ inch drop below the optimum level. Thus, the critical problem of maintaining blood level was minimized. Oxygenation of the blood was in no way compromised by utilization of the coil.

Bubble formation during rapid rewarming did not present a major problem. In 2 of the 23 cases, small bubbles were noted in the plenum chamber at the end of the experiment; however, these 2 animals presented no neurological deficits and were long-term survivors.

In this series of 23 animals, all survived at least 18 hours. Fourteen were considered long term, surviving longer than 72 hours. No neurological symptoms were present in any animal and all deaths were unrelated to the hypothermia.

Clinical Results.—This method has been successfully employed clinically for total extracorporeal hypothermia in 12 patients and for maintenance of normothermia in 5 others at the Naval Hospital, Bethesda, Maryland. The same evaluation and monitoring apparatus used in the laboratory were incorporated in its clinical application.

The decision to use hypothermia was made following thoracotomy and after total cardiopulmonary bypass had been instituted. Duration of perfusion ranged from 30 to 52 minutes. No additional operative or perfusion time was required for the cooling or rewarming.

In these cases the esophageal temperature was lowered 1.0° to 2.6° C. per minute and was rewarmed 0.5° to 1.0° C. per minute. Esophageal temperatures were maintained at 28° to 29° C. The average plasma hemoglobin increase was 35 mg. per cent and the platelet decrease was 50 per cent of preoperative values.

DISCUSSION

This type of extracorporeal thermoregulation provides a highly efficient and safe method for rapid total body cooling and rewarming. It supplies the cardiovascular surgeon with immediate hypothermia at any time during an operation without committing him to it preoperatively. Minimal operating time need be wasted cooling and rewarming. Rapid cooling can be effected in cases of unexpected high flows which exceed the capacity of the oxygenator. If

cerebral emboli are suspected during a procedure, protection with immediate hypothermia is available.

Increased efficiency of body cooling and rewarming is achieved by utilizing this apparatus within the oxygenator. This, also, eliminates additional units in the circuit with their increased impedance to blood flow and larger priming volume. Maximum safety is achieved because the oxygenator serves as a bubble trap for any gases released during rapid rewarming, and the coil permits wider fluctuation of the blood level without frothing.

The higher velocity of cooling (2.9° C. per minute) compared to rewarming (1.0° C. per minute) is largely due to the greater gradient which can be applied in cooling. Coil temperature of 1.5° C. applied to 37° C. blood yields a 33.5° C. differential operating in favor of the desired temperature change. However, a 44° C. coil temperature contacting 20° C. blood during rewarming allows only a 24° C. gradient. In addition, warming must overcome the effect of 25° C. room temperature. The normal temperature regulation mechanism of the animal does not play a large role with this "core" method of thermoregulation. With the high efficiency of heat exchange, the larger flows per unit weight produce faster rates of "core" temperature change (see Figs. 4 and 5). Total weight seems to make no difference within the range employed. Application for clinical hypothermia in 70 Kg. patients has produced equal or faster rates of temperature change than in animals. Differences in the cooling or rewarming rate of animals with the same weight, blood flow, and inflow blood temperature may be due to variations in vasoconstriction or in fat distribution.

The 50 per cent reduction of blood flow in the extracorporeal circuit below 30° C. is substantiated by the observation of King and Bounos[12] that cardiac input is 48 per cent of the normal at that temperature.

The "core" method of hypothermia cools the vital organs rapidly and the muscle mass slowly. Thus, the more vascular organs with high oxygen demands are afforded hypothermic protection early which is an advantage over the surface cooling techniques.

During hypothermia, the cooler, more viscous blood decreases the output of the Tygon pumping bag in our system approximately the same amount as the venous inflow to the oxygenator is reduced. This eliminates the necessity for change in the pump control settings during cooling or rewarming despite the marked variation of blood flow.

The theoretical possibility that dissolved oxygen will come out of solution on rapid blood rewarming and produce emboli is based on the fact that the solubility of a gas is inversely proportional to the temperature; that is, at 2° C., twice as much oxygen is soluble in plasma as at 37° C. The plenum chamber was employed because it is the most sensitive method of detecting microscopic bubbles in a flowing stream, according to Maloney.[13] Our experiments substantiated this fact, since the direct examination of blood film with a microscope or the decompression of organs proved cumbersome and less reliable.

Neither of the animals in which small bubbles were demonstrated in the plenum trap during rapid rewarming exhibited neurological signs. Since this represents only 9.1 per cent of our series and both of these animals were long-term survivors, it is concluded that rapid blood rewarming, providing it is done

within an oxygenator, is safe. In clinical use, a maximum gradient of 20° C. has been utilized in order to remain well within the limits of safety.

SUMMARY

1. A highly efficient method for direct blood cooling and rewarming, utilizing the rotating disc oxygenator and employing an electronically controlled thermoregulation unit, has been presented.

2. Blood temperatures are reduced at 16° C. per minute and rewarmed at 9° C. per minute with precise control and safety. Esophageal temperatures may be lowered 2.9° C. per minute and rewarmed 1.0° C. per minute.

3. Successful clinical application of this method for rapid hypothermia produced with total cardiopulmonary bypass has been made in 5 patients.

4. Blood may be exposed to temperatures of 1° C. for cooling and temperatures of 45° C. for warming without significant blood element damage.

5. Rapid rewarming of cold oxygenated blood does not produce experimentally or clinically significant gas emboli with this method.

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THE CLINICAL USE OF POLYBRENE AS AN ANTIHEPARIN AGENT IN OPEN HEART SURGERY

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INTRODUCTION

THE USE of extracorporeal circulation demands that the blood of the patient be reliably anticoagulated. The agent commonly used is heparin. It is, of course, necessary to re-establish the clotting mechanism at the end of the bypass period. Until recently, the only antiheparinic agents available were protamine (Salmine) sulfate and toluidine blue. Now a new agent is available which shows considerable clinical promise. The purpose of this paper is, first, to review mainly the undesirable effects of protamine, and, second, to review our clinical experience with the newer agent, Polybrene.*

THE ANTIHEPARIN ACTIVITY OF PROTAMINE (SALMINE) SULFATE

The antiheparin activity of protamine was described as early as 1937 by Chargraff and Olson,[1] but was not clinically employed until heparin was employed more vigorously in the treatment of various thromboembolic phenomena. The need for rapid reversal of the anticoagulant effect of heparin was seldom necessary. However, the advent of open heart surgery, utilizing cardiopulmonary bypass techniques, has brought with it the need for rapid reversal of heparin effect, and thus the widespread use of protamine.

Although protamine is usually an effective agent, there are several factors worthy of mention which render it less than ideal. First, and requiring little explanation, the relative instability of the preparation is an undesirable quality. Second, the paradoxical anticoagulant activity of protamine places upon the physician the onus of relatively accurate calculation of dosage by rather laborious methods. This anticoagulant effect of protamine seems multifaceted. Portman and Holden,[2] and Hougie[3] demonstrated that protamine interferes

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with the conversion of prothrombin into thrombin. Hougie states that, in low concentration, protamine is antithromboplastinogenic. These authors also describe the inactivation of fibrinogen by protamine. This reaction presumably takes place by the formation of a soluble protamine-fibrinogen complex. The complex thus formed is somewhat analogous to that formed in the interaction of the macromolecular plasma expanders (polyvinylpyrrolidone, Dextran) and fibrinogen. Jacques,[4] in 1949, verified that, up to a certain level, protamine reverses the anticoagulant effect of heparin, but beyond this level, it seems to enhance the heparin effect.

Third, Jacques further demonstrated that the rapid infusion of protamine causes a marked fall in the blood pressure, probably as a result of the extensive dilatation of muscular arterioles. This fall in blood pressure is sometimes resistant to therapy in experimental animals and seems increased in those who have undergone extracorporeal circulation.[5] Jacques also reported the transient leukopenia and thrombocytopenia following the injection of protamine. The extent of the deleterious nature of this reduction in number of formed elements of the blood is unclear.

Fourth, it would be desirable to have an antiheparin agent which would exert an in vivo anticoagulant effect more quickly than protamine. Although in vitro the reversal of heparin with protamine is instantaneous, limitations in the rate of administration delay the in vivo appearance of clotting.

A fifth criticism of protamine rests with the varying potency of the preparation. This factor renders the establishment of standard doses virtually impossible. Portman and Holden found that the protamine/heparin ratio in vitro varied from 16:1 to 0.7:1.0, depending upon the particular lot of protamine used.

With these inadequacies in mind, several relatively satisfactory methods have been suggested to estimate the amount of protamine required to reverse the heparin effect. All of these are variants of the titration techniques. These techniques, however, are time consuming, and thus constitute another criticism to the clinical use of the preparation.

A BRIEF DESCRIPTION OF POLYBRENE

It is understandable that the description of a new antiheparin agent in 1953 was welcomed.[5] This material, Polybrene, is a stable quartenary ammonium salt with a formula $(C_{13}H_{30}Br_2N_2)_x$, a polymer of N,N,N^1,N^1 tetramethyl-hexamethylenediamine and trimethyl bromide. It shares features with both protamine and toluidine blue. It exerts a potent antiheparin effect both in vivo and in vitro. It is also in itself an anticoagulant.

A clinical and experimental trial of Polybrene has been reported by Weiss and his associates.[7] This group concluded that the agent is superior to protamine and toluidine blue. They reported rapid conversion to a normal clotting time, with minimal side effects. These include dizziness, thought to be secondary to a transient hypotension from too rapid administration. The authors also considered the possible antigenic role of Polybrene, and advised against its use in patients with a history of allergic response.

TABLE I. A SUMMARIZATION OF THE USE OF POLYBRENE TO REVERSE THE HEPARIN EFFECT IN 47 PATIENTS

NO.	WT. (KG.)	HEPARIN (MG.)	POLYBRENE (MG.)	RATIO HEPARIN/ POLYBRENE	TIME BETWEEN HEPARIN AND POLYBRENE (MIN.)	MIN. AFTER POLYBRENE TO CLOTTING TIME DETER.	CLOTTING TIME (MIN.)	REMARKS
1	43	50	35	1.4/1	—	10	10	No reaction
2	15	30	21	1.4/1	—	10	9	No reaction
3	56	170	120	1.4/1	—	(a) 30	(a) 75	Given additional 50 mg. Polybrene
						(b) 55	(b) 20	No reaction
4	54	160	115	1.4/1	—	(a) 30	(a) 25	Stridor, general rash; I.V. Benadryl
						(b) 60	(b) 6	Additional 20 mg. Polybrene
5	41	124	100	1.2/1	—	75	16	No reaction
6	15	45	40	1.1/1	—	10	12	No reaction
7	52	160	120	1.4/1	—	10	13	No reaction
8	66	210	150	1.4/1	—	(a) 10	(a) 21	No reaction
						(b) 55	(b) 11	Additional 60 mg. Polybrene
9	—	180	140	1.3/1	—	15	15	No reaction
10	—	150	130	1.2/1	90	15	25	Additional 50 mg. Polybrene
11	—	190	190	1.0/1	—	15	7	No reaction
12	12	96	60	1.6/1	—	(a) 15	(a) 18	No reaction
						(b) 45	(b) 5	Additional 30 mg. Polybrene
13	58	180	180	1.0/1	110	15	15	No reaction, patient on lipoheparin preop.
14	20	60	60	1.0/1	60	20	7	No reaction
15	56	170	170	1.0/1	127	(a) 25	(a) 26	Patient with
						(b) 60	(b) 23	severe clotting disorder; given 32 L. whole blood, additional 170 mg. Polybrene
16	70	240	240	1.0/1	190	15	5	No reaction
17	6	20	20	1.0/1	96	15	8	No reaction
18	56	170	170	1.0/1	87	10	20	No reaction
19	26	80	80	1.0/1	73	20	5	No reaction
20	65	210	210	1.0/1	125	20	8	No reaction
21	60	200	200	1.0/1	210	18	12	No reaction
22	60	200	200	1.0/1	155	15	10	No reaction
23	48	150	150	1.0/1	90	20	10	No reaction
24	62	150	150	1.0/1	95	15	6	No reaction
25	8	30	30	1.0/1	100	(a) 25	(a) 25	No reaction
						(b) 55	(b) 10	Additional 10 mg. Polybrene
26	55	170	170	1.0/1	85	20	8	No reaction
27	24	80	80	1.0/1	75	15	15	No reaction
28	33	100	100	1.0/1	80	15	8	No reaction
29	80	240	240	1.0/1	66	(a) 15	(a) 30	Additional 100
						(b) 45	(b) 8	mg. Polybrene, urticarial rash, I.V. Benadryl
30	50	160	160	1.0/1	65	15	15	No reaction
31	42	150	150	1.0/1	89	20	10	No reaction
32	72	220	220	1.0/1	85	15	9	No reaction
33	11	33	33	1.0/1	105	15	7	No reaction

TABLE I—CONT'D

NO.	WT. (KG.)	HEPARIN (MG.)	POLYBRENE (MG.)	RATIO HEPARIN/ POLYBRENE	TIME BETWEEN HEPARIN AND POLYBRENE (MIN.)	MIN. AFTER POLYBRENE TO CLOTTING TIME DETER.	CLOTTING TIME (MIN.)	REMARKS
34	29	90	90	1.0/1	168	15	9	No reaction
35	10	30	30	1.0/1	95	20	9	No reaction
36	37	120	120	1.0/1	100	15	10	No reaction
37	32	110	110	1.0/1	81	(a) 15	(a) 25	No reaction
						(b) 35	(b) 10	Additional 50 mg. Polybrene
38	74	230	230	1.0/1	177	15	8	No reaction
39	47	140	140	1.0/1	75	15	7	No reaction
40	45	140	140	1.0/1	90	15	8	No reaction
41	52	160	160	1.0/1	75	15	7	No reaction
42	24	70	70	1.0/1	95	15	8	No reaction
43	53	160	160	1.0/1	60	15	13	No reaction
44	68	200	200	1.0/1	75	15	15	No reaction
45	82	200	200	1.0/1	95	15	8	No reaction
46	28	60	60	1.0/1	20	15	7	No reaction
47	91	300	300	1.0/1	175	15	5	No reaction

Five factors indicate that Polybrene has many advantages over the older antiheparinic agents: (1) its stability, (2) its apparent more rapid action, (3) the apparent greater margin of safety between doses which have a good antiheparin effect and those which might exert a synergistic anticoagulant activity, (4) the uniform potency of the preparation from one lot to another, and (5) the absence of severe hypotensive reactions.

THE CLINICAL USE OF POLYBRENE

In the first 52 cases of open heart surgery done at this institution, protamine was routinely used to reverse the heparin effect. In view of the encouraging factors already reviewed concerning Polybrene, beginning over a year ago that preparation has been used exclusively as an antiheparin agent in patients undergoing open heart surgery. It has now been employed in 47 cases, a summary of which has been tabulated in Table I. Although a careful record of the clotting time was not routinely kept when protamine was employed, these clotting times were frequently prolonged after heparin effect reversal, regardless of the amount of protamine used. In contrast, the rapidity and consistency of reversal of the heparin effect by Polybrene has been striking.

In the first 12 cases, a heparin/Polybrene ratio (milligram to milligram) of 1.4:1.0 was employed. This was in accord with the ratio suggested by Preston and others.[6] However, in 9 of these cases, the clotting time, as determined by a modified Lee and White technique, was greater than 10 minutes, when measured from 10 to 25 minutes after the administration of the Polybrene. In 5 of these cases, the clotting time was sufficiently prolonged (up to 75 minutes), and the patient's bleeding of such a magnitude, that additional Polybrene was given (up to 60 mg.). In these 9 cases, the second determination of the clotting time was satisfactory, and the patient showed

evidence of clotting clinically. These augmenting doses were noted to bring the heparin/Polybrene ratio to 1.0:1.0. Consequently, since that experience, Polybrene has been administered on a milligram per milligram basis with heparin.

Although some observers have reported a transient, albeit sometimes rather marked hypotension following the intravenous administration of Polybrene, the phenomenon has not been observed with constantly monitored arterial pressures. An attempt has been made to give the calculated dose slowly into the infusion line over a period of approximately 5 minutes. In a few instances, however, this period has been substantially reduced without any untoward effect being noted.

In the last 35 cases, supplemental Polybrene was given in four instances. The first, Case 15, was a 19-year-old boy with a tetralogy of Fallot, who had previously undergone a Blalock procedure. One hundred and seventy milligrams of heparin was administered for anticoagulation followed by a like amount of Polybrene 127 minutes later. Bleeding from all areas of the incision however, continued to be massive; and the clotting time, as measured 25 minutes after Polybrene administration, was 26 minutes. An additional 170 mg. of Polybrene was given, yet 20 minutes later the clotting time was 25 minutes. During this period, the sternotomy incision was re-opened in an attempt to control local bleeding points. It was obvious that a diffuse hematologic defect existed. A *total* of 32 L. of fresh whole blood was given to this patient. He died with continued massive blood loss, in spite of fresh blood, fibrinogen, vitamin K, steroids, and adrenochrome semicarbazone. This bleeding diathesis was evident prior to administration of Polybrene, and, in view of the massive transfusions necessitated by continued blood loss, this case cannot be regarded as a Polybrene failure. The hemorrhagic disorder could not be clearly defined by the hematologists prior to the patient's death.

A second instance in which additional Polybrene was given was that of Case 29, a 33-year-old man weighing 80 kilograms, who had a ventricular septal defect. Two hundred and forty milligrams of heparin was administered 66 minutes before the patent received an equal amount of Polybrene. The clotting time, as measured 15 minutes after the administration of Polybrene, was 30 minutes. He received an additional 100 mg. of the agent (total dose—340 mg., or 4.25 mg./Kg.), with a second clotting time determination of 8 minutes. Shortly after receiving the supplemental Polybrene, this patient developed a generalized urticarial rash, which rapidly cleared. This reaction cannot be clearly connected to the Polybrene, as the continued bleeding had necessitated the administration of considerable blood subjected to a 10-minute emergency crossmatch. The postoperative course was without incident.

Another case which warrants mention is that of a 20-year-old woman with an uncomplicated atrial septal defect (Case 4). She received 160 mg. of heparin prior to cardiopulmonary bypass, followed by 115 mg. of Polybrene

at decannulation. Restoration of a normal coagulation mechanism was prompt and lasting. However, the patient developed a generalized erythematous papular rash and a minimal stridor. These complications were first noted 45 minutes after administration of Polybrene, when the drapes were removed and the patient extubated. It was thought that the stridor was possibly due to vocal cord trauma at the time of intubation, or to drug or transfusion reaction. Because it was believed that if this respiratory difficulty became worse on the ward, the patient's life might be compromised, a tracheostomy was performed while she remained in the operating room. Shortly thereafter, on occlusion of the tracheostomy tube, no stridor was noted. When the tube became dislodged after a forceful cough that evening, it was decided to leave it out. Again, the convalescent period was uneventful.

The other patients requiring an additional amount of Polybrene received it without incident, with a rapid reversion to a normal clotting time. There have been no instances other than the rather inconclusive ones described above of any reaction associated with Polybrene administration. In one instance, Case 46, that of a child found to have an inoperable congenital lesion upon digital exploration of the heart, the antagonistic dose of Polybrene was given just 20 minutes after an equivalent amount of heparin. The clotting time, as measured 15 minutes later, was just 7 minutes. As seen in Table I, the clotting time, measured 15 minutes after Polybrene administration, has been consistently below 15 minutes and, in 80 per cent of cases, under 10 minutes.

SUMMARY

Protamine reversal of the anticoagulant effect of heparin was used in approximately the first half of 100 patients undergoing open heart surgery at this institution. In the last 47 patients, Polybrene has been utilized for this purpose. The superiority of Polybrene seems unequivocal.

The clotting time, measured 15 minutes after Polybrene administration, was between 5 to 10 minutes in 80 per cent of the patients, and consistently below 15 minutes in all patients without complicating factors. Two patients developed a maculopapular rash not clearly related to Polybrene administration. Both responded readily to intravenous Benadryl. The ratio of 1.0 mg. of Polybrene to 1.0 mg. of heparin has been most effective. Only occasionally has additional Polybrene been necessary to obtain the desired effect.

The main advantages of this drug over others with similar action are fivefold: (1) stability, (2) its apparent more rapid action, (3) the apparent greater margin of safety between doses which have a good antiheparin effect and doses which might exert a synergistic anticoagulant effect, (4) the uniform potency of the preparation, and (5) the absence of severe hypotensive reactions.

The combination of these attributes and this experience indicate the value of Polybrene in open heart surgery, and whenever rapid complete reversal of the heparin effect is desired. It is now routinely used in this clinic for this purpose.

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EXPERIMENTAL STUDIES WITH EXTRACORPOREAL CIRCUITS AS A METHOD TO ENABLE SURGICAL ATTACK ON THORACIC ANEURYSMS

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SINCE GROSS'S work with aortic coarctation[1, 2] a decade ago, surgeons have been occupied devising reconstructive surgical procedures to deal with diseases of the thoracic aorta. While the generous collateral circulation around a coarctation allows clamping of the aorta proximal and distal to the lesion and performance of surgery in a dry field without urgency, the absence of collateral circulation about aneurysms or acute lesions of the thoracic aorta poses two major problems which become increasingly significant the closer to the heart the aorta is clamped. The first is the problem of ischemic injury to structures supplied by the aorta, distal to the point of occlusion. The second is the effect of occlusion on proximal structures, that is, hypertension in the proximal aorta, left ventricular strain, and embarrassment of coronary flow if the occluding clamp is very close to the heart. Bahnson[3] was able to sidestep these difficulties in certain thoracic aortic aneurysms by performing reconstructive aneurysmorraphy with a lateral nonoccluding aortic clamp. This method, however, will be effective only in truly saccular aneurysms and, because of lack of aortic control, may lead to difficulties where the aneurysm has eroded into adjacent structures. Cooley and his associates[4] have been able to resect and replace segments of aortic arch by the use of shunts sutured to the ascending aorta, bypassing the lesion, but this limits access to ascending aortic lesions. They have also dealt with lesions of the proximal aorta by use of the pump-oxygenator and total body perfusion.[5, 6] This complicates the procedure by the addition of a mechanical oxygenator although the patient's own lungs remain potentially useful. This group has exploited the patient's lungs in lesions of the descending aorta by pumping directly from the left auricle to the femoral artery, omitting the oxygenator, but has confined the use of this technique to bypass of the distal thoracic aorta.[6, 7]

The present animal study was undertaken to evaluate various methods of shunting or pumping blood past isolated segments of thoracic aorta, considering separately the descending aorta, the entire aortic arch, and the ascending aorta.

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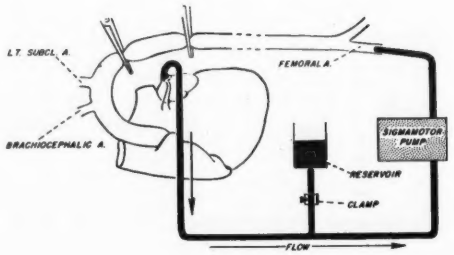


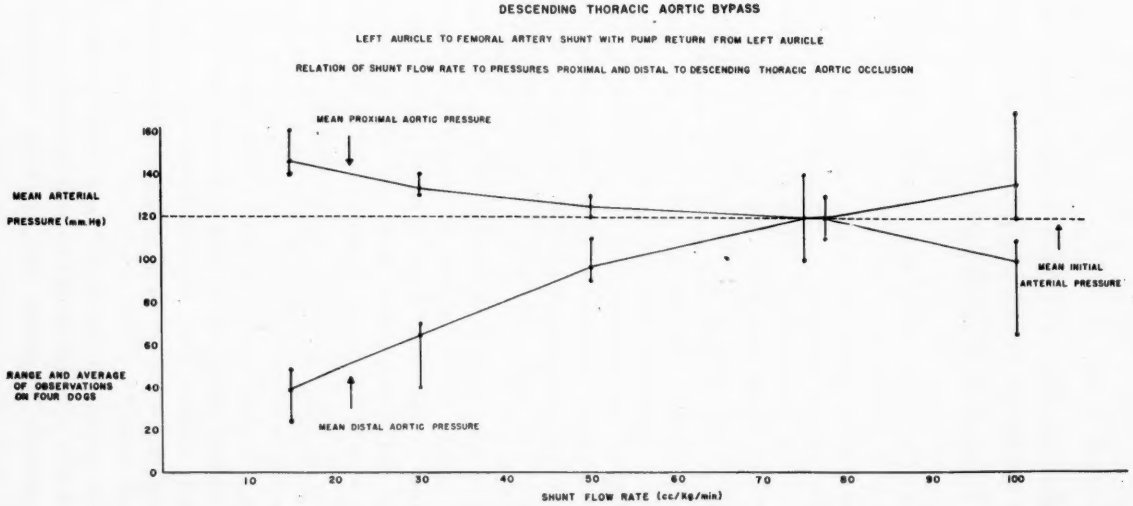


Fig. 1.—*Descending thoracic aortic bypass employing a left auricle to femoral artery shunt with pump return from the left auricle.* By this system oxygenated blood is removed by active suction from the left auricle and supplies the distal visceral structures via the femoral artery. The aorta proximal to the point of obstruction is perfused as in the normal. It is possible to obtain physiologic flows and essentially normal pressures proximal and distal to the point of aortic occlusion, by this method.

This requires determinations of the rate of shunt flow needed to perfuse structures distal to the point of obstruction and to decompress the proximal aorta without depriving it of too much blood. In each of the three aortic levels, the shunting method most simple and feasible for human work was sought.

METHOD

Mongrel dogs were anesthetized with Pentothal (thiopental sodium) and prepared by the administration of 1.5 mg. heparin per kilogram of body weight. In all dogs, the duration of aortic occlusion and bypass was 90 minutes. In survival experiments the dog was considered intact if, at the end of 1 week, the behavior and activity of the dog were grossly normal, and if creatinine clearance and maximal osmotic concentrating power of the kidneys were comparable to preoperative values. Mean arterial pressures were determined proximal and distal to the point of aortic occlusion by either pressure transducers and recording equipment, or simply by measuring with an aneroid pressure gauge connected to the vessel through an air column. Shunt flows were measured by passing the shunted blood through a calibrated Sigmamotor pump. The relations between pressure and flows in such experiments were greatly affected by reflex alterations in vasomotor tone. These changes were minimized by carrying the animals at deep levels of anesthesia. For similar reasons, effort was made to maintain the dog's blood volume at its initial level, erring on the high side.

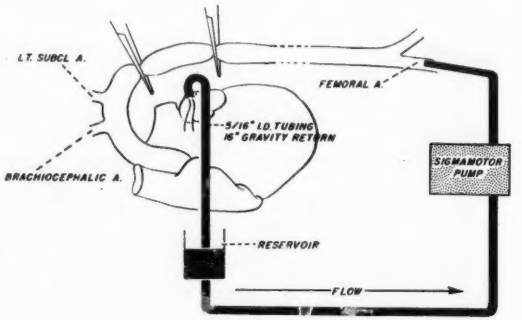
Free hemoglobin was determined immediately after the runs by the spectrophotometric method described by Hunter, Grove-Rasmussen, and Soutter.[8]

Descending Aorta Bypass.—

Four shunting arrangements were tested: (1) actively pumping from the left auricle to the femoral artery with the application of suction to the left auricle, (2) gravity flow from the left auricle to a reservoir, thence pumping to the femoral artery, (3) actively pumping from the subclavian artery to femoral artery, with the application of suction to subclavian artery catheter, and (4) simple subclavian artery–femoral artery shunt.

1. *Left auricle to femoral artery shunt with pump return from the left auricle:* This apparatus is shown in Fig. 1. Oxygenated blood is actively pumped from the left auricle to the femoral artery by applying suction to the left auricle with a Sigmamotor pump. An emergency reservoir, attached by a T connection to the inflow side of the pump and ordinarily clamped off, is not essential, but is a convenient means of rapid transfusions with donor blood or with blood recovered from the subject.

Fig. 1 shows the effect of varying shunt flow rate on mean arterial pressure, proximal and distal to the point of aortic occlusion. It will be noted that these two pressures are equal and also approximate the aortic pressure before occlusion at a flow of about 75 c.c./Kg./min., which presumably defines unobstructed flow at this level in the aorta. Flows less than this ideal are allowable



DESCENDING THORACIC AORTIC BYPASS

LEFT AURICLE TO FEMORAL ARTERY SHUNT WITH GRAVITY RETURN FROM LEFT AURICLE

MEAN PRESSURE (mm.Hg.) DATA, SHUNT FLOW, AND SURVIVAL RESULTS FOR NINETY MINUTE DESCENDING THORACIC AORTIC BYPASS

DOG NO.	MEAN PRESSURE IN PROXIMAL AORTA		MEAN PRESSURE CHANGE IN PROXIMAL AORTA	MEAN PRESSURE IN DISTAL AORTA		MEAN PRESSURE CHANGE IN DISTAL AORTA	FLOW IN SHUNT cc/Kg./min.	SURVIVALS	COMPLICATIONS					Hgb. CONC. AT NINETY MINUTES (mg.%)
									NEURO-LOGICAL	UROLOGICAL				
	BEFORE BYPASS	DURING BYPASS		BEFORE BYPASS	DURING BYPASS					CONC. POWER (mosm./L) PRE-OP	POST-OP	CREAT. CLEARANCE (cc/min) PRE-OP	POST-OP	
5	130	145	+15	130	40	-90	30	YES	normal	2000	2200	90	95	—
6	120	140	+20	120	70	-50	30	YES	normal	2100	1900	100	90	—
7	125	150	+25	125	70	-55	30	YES	normal	2300	2400	90	95	40
8	110	120	+10	110	65	-45	30	NO	—	—	—	—	—	35
9	120	130	+10	120	50	-70	30	YES	normal	1800	2100	90	90	30
10	100	110	+10	100	80	-20	30	YES	normal	2200	1900	85	90	35
AVERAGE	118	133	+15	118	63	-55								

Fig. 2.—*Descending thoracic aortic bypass employing a left auricle to femoral artery shunt with gravity return from the left auricle.* This system is similar to that shown in Fig. 1, but blood is syphoned rather than pumped from the left auricle. At moderate flow rates it is possible to decompress the proximal aorta, adequately perfuse the distal viscera, and obtain a high rate of survival after 90-minute shuntings.

and, in practice, would stress the system less and involve less pumping trauma to the blood. A flow of 30 c.c./Kg./min. may be a reasonable minimum, resulting in a proximal pressure rise of about 16 mm. Hg and distal drop of 55 mm. Hg to a mean of 65 mm. Hg. At flow below this level, not only does the distal pressure drop to precariously low levels, but the proximal pressure rises to dangerously high values. At flows much in excess of 75 c.c./Kg./min. the demand of the pump exceeds the flow into the auricle, and the tubing on the inflow side of the pump collapses. Four consecutive dog subjects were shunted for 90 minutes at the previously stated minimum flow rate of 30 c.c./Kg./min. Survival of the animals was attempted to evaluate adequacy of visceral perfusion under these circumstances. All dogs survived and showed no evidence of injury at 1 week. Hemoglobin concentrations at the end of the 90-minute run in these dogs were approximately 35 mg. per cent.

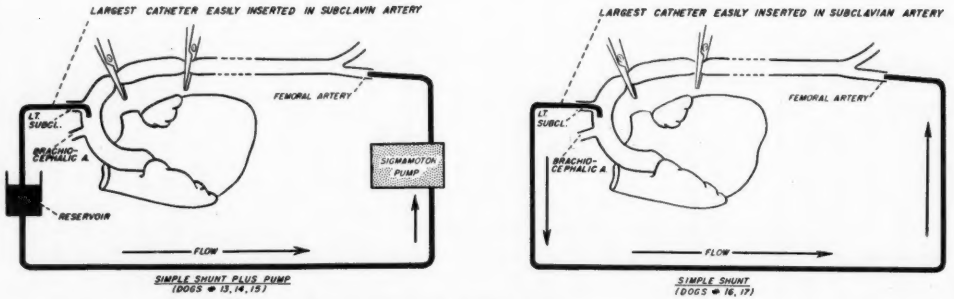
2. *Left auricle to femoral artery shunt with gravity return from the left auricle:* This apparatus is shown in Fig. 2. Here a collecting inflow reservoir is intrinsic in the apparatus. A greater priming volume is required, and flow rates are determined and limited by the size of tubing used and hydrostatic pressure head available in the syphon. Flows are thus determined by purely hydraulic considerations and can be predicted by reference to Fig. 9, which shows the relation of flow rate to inflow tubing size and pressure head. With the apparatus used, the maximum flows obtainable ranged from 60 to 70 c.c./Kg./min. in the 6 dogs run. Ninety-minute shuntings at the previously stated minimum flow of 30 c.c./Kg./min. were made in 6 dogs. Five dogs showed no evidence of injury at the end of 1 week. One dog died of hemothorax and massive atelectasis at the end of 4 hours.

3. *Simple subclavian artery to femoral artery shunt without pump return from the subclavian artery:* The apparatus used is shown in Fig. 3. In 3 dogs, the subclavian catheter was allowed to bleed into a collecting reservoir in order that flows could be measured by means of the calibrated pump. These flows were below the previously defined minimum of 30 c.c./Kg./min. and could only have been lower had the simple subclavian artery to femoral artery shunt, which the apparatus was intended to simulate, been used. Two additional dogs were run using the simple shunt, and pressure levels were comparable.

Of these 5 dogs, 4 survived, 1 dying of hemorrhage a few hours after the experiment. Of these 4 surviving dogs, 2 were in good condition at the end of 1 week and 2 showed evidence of renal injury.

This limitation of flow is obviously due to the small caliber of the arterial catheters and the limited pressure available in the proximal aorta, and could be avoided by subclavian or aortic cannulation using larger tubing. However, the relative simplicity and ease of inserting small subclavian and femoral artery catheters make this a desirable shunting circuit past descending aortic lesions, if flows could be made adequate.

4. *Subclavian to femoral artery shunt with pump return from the subclavian artery:* The arrangement shown in Fig. 4 was used in an effort to overcome the insufficient flows of the simple subclavian artery to femoral artery



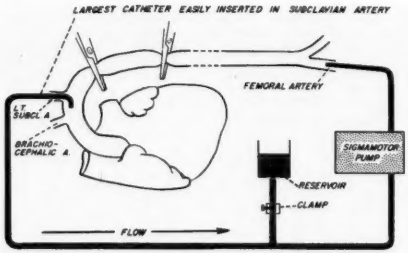
DESCENDING THORACIC AORTIC BYPASS

SUBCLAVIAN TO FEMORAL ARTERY SHUNT WITHOUT PUMP RETURN FROM SUBCLAVIAN

MEAN PRESSURE (mm/Hg.) DATA, SHUNT FLOW AND SURVIVAL RESULTS FOR NINETY MINUTE DESCENDING AORTIC BYPASS

DOG NO.	MEAN PRESSURE IN PROX. AORTA BEFORE BYPASS	MEAN PRESSURE IN PROX. AORTA DURING BYPASS	MEAN PRESSURE CHANGE IN PROX. AORTA	MEAN PRESSURE IN DISTAL AORTA BEFORE BYPASS	MEAN PRESSURE IN DISTAL AORTA DURING BYPASS	MEAN PRESSURE CHANGE IN DISTAL AORTA	FLOW IN SHUNT cc/Kg./min.	SURVIVALS %	COMPLICATIONS					HEMOGLOBIN CONC. AT NINETY MIN. (mg %)
									NEUROLOGICAL	UROLOGICAL				
										CONC. POWER (mosm/L.) PRE-OP	POST-OP	CREAT. CLEARANCE (cc/min.) PRE-OP	POST-OP	
13	120	150	+30	120	40	-80	25	NO	normal	—	—	—	—	—
14	110	140	+30	110	40	-70	20	YES	normal	2000	1900	90	95	40
15	110	145	+35	110	35	-75	15	YES	normal	2100	*1800	90	* 60	—
16	120	150	+30	120	30	-90	unknown	YES	normal	2200	*1380	85	* 55	—
17	130	140	+30	130	35	-95	unknown	YES	normal	2400	2200	90	100	20
AVERAGE	118	149	+31	118	35	-82								* ABNORMAL RENAL FUNCTION

Fig. 3.—*Descending thoracic aortic bypass employing a subclavian to femoral artery shunt without pump return from the subclavian.* Here the subject's arterial pressure provides the impetus for shunt flow. This system gives only marginal flow rates and results in high proximal pressures and, on occasion, inadequate distal perfusion.



DESCENDING THORACIC AORTIC BYPASS

SUBCLAVIAN TO FEMORAL ARTERY SHUNT WITH PUMP RETURN FROM SUBCLAVIAN

RELATION OF SHUNT FLOW RATE TO PRESSURE PROXIMAL AND DISTAL TO DESCENDING AORTIC OCCLUSION

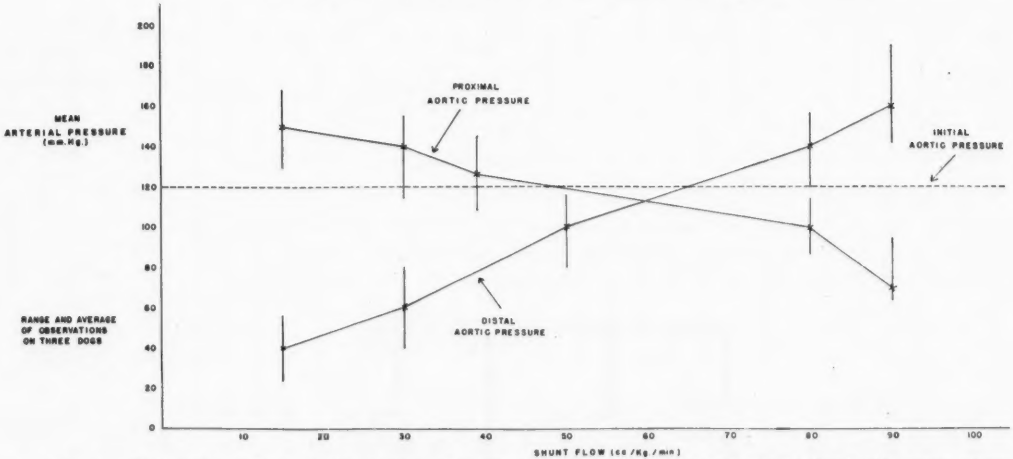
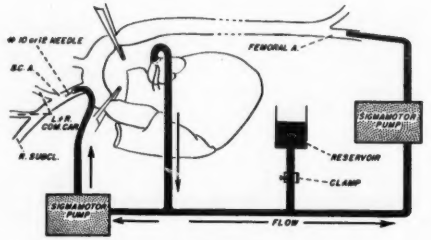


Fig. 4.—*Descending thoracic aortic bypass employing a subclavian to femoral artery shunt with pump return from the subclavian artery.* The subject's arterial pressure is complemented by a pump to provide a greater impetus to shunt flow. It is possible to obtain physiologic flows and essentially normal pressures, proximal and distal to the aortic occlusion, by this method.



AORTIC ARCH BYPASS

LEFT AURICLE TO FEMORAL AND BRACHIOCEPHALIC ARTERIES WITH PUMP RETURN FROM LEFT AURICLE

RELATION OF SHUNT FLOW RATE TO PRESSURE PROXIMAL AND DISTAL TO AORTIC ARCH OCCLUSION

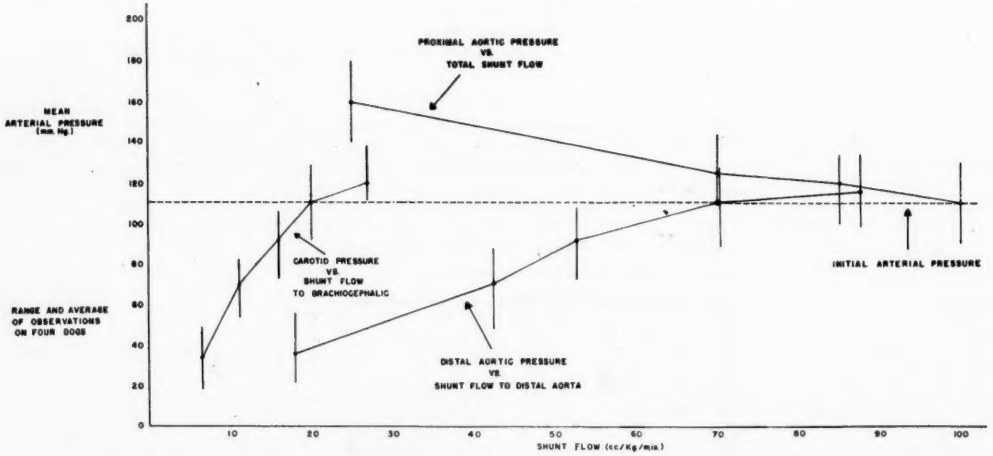


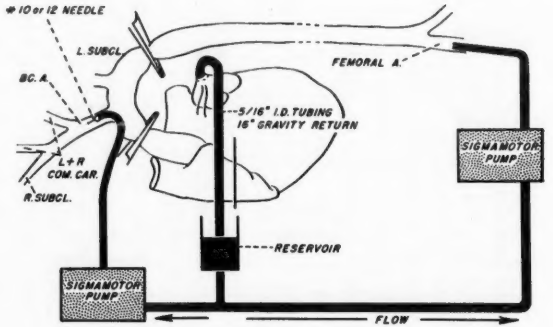
Fig. 5.—*Aortic arch bypass employing a left auricle to femoral and brachiocephalic arteries shunt with pump return from the left auricle.* Oxygenated blood is removed by active suction from the left auricle and supplies the distal visceral structures and cerebrum via the femoral and brachiocephalic arteries, respectively. The residual left auricular blood passes through the left ventricle and supplies the coronary vessels. It is possible to obtain physiologic flows and essentially normal pressures, proximal and distal to the aortic occlusion, by this method.

shunt by the interposition of a pump. Five dogs were run; 3, in order to explore possible flows, and the last 2 to test survival with the 30 c.c./Kg./min. flow. The effect of various flows on proximal and distal aortic pressure corresponds with the data obtained from the similar study with left auricle to femoral artery shunt. It is quite possible to obtain high flows in the dog in this manner. Two surviving dogs showed no ill effects at 1 week.

Arch of Aorta Bypass.—

Two shunting arrangements were tested: (1) active pumping from the left auricle to the femoral artery and the brachiocephalic artery with the application of suction to the left auricle; and (2) gravity flow from the left auricle to a reservoir, thence pumping to the femoral artery and brachiocephalic artery.

1. *Left auricle to femoral and brachiocephalic arteries with pump return from left auricle:* This apparatus is shown in Fig. 5. An additional pump is used in this system to supply the brachiocephalic artery and thence both carotids and the right vertebral artery. A No. 10 or 12 needle is used in the dog subjects to perfuse the brachiocephalic artery because this is large enough for the flow required but not so large as to occlude completely the artery at a time when the extracorporeal circuit is not in use. Fig. 5 shows the effect of varying flow rate on mean arterial pressure, proximal and distal (aorta and carotid) to the point of aortic occlusion. It will be noted that these three pressures are equal and also approximate the aortic pressure before occlusion at a flow of about 100 c.c./Kg./min. (20 to 25 c.c./Kg./min. to the head and 70 to 75 c.c./Kg./min. to the rest of the subject). Once again flows less than this ideal are allowable and probably desirable. Sixty cubic centimeters per kilogram per minute (15 c.c./Kg./min. to the head and 45 c.c./Kg./min. to the rest of the subject) may be a reasonable minimum, resulting in a proximal pressure rise of 26 mm. Hg and a distal pressure drop in the carotids and aorta of 40 mm. Hg to a pressure of 70 mm. Hg. At flows below this level not only did the distal pressures drop to precariously low levels but the proximal aortic pressure rose to dangerously high values; at flows below 40 c.c./Kg./min., evidence of left ventricular strain occurred, cardiac action became irregular, and cardiac arrest or ventricular fibrillation ensued within 5 minutes in almost every case. Even at 60 c.c./Kg./min., cardiac irregularities sometimes occurred in the initial period after aortic occlusion, but these signs usually disappeared within 10 minutes, if the catheter was correctly positioned to obtain adequate outflow. On occasion it was necessary to place the catheter through the mitral valve. In all cases of proximal aortic occlusion it was essential to make multiple vents in the catheter to avoid outflow obstruction. At flows much in excess of 100 c.c./Kg./min., the demand of the pump exceeded the flow into the auricle and the tubing on the inflow side of the pump would collapse. Ninety-minute shuntings at the previously stated minimum flows of 60 c.c./Kg./min. were made in 2 dogs and survivals were attempted in order to evaluate adequacy of this type



AORTIC ARCH BYPASS

LEFT AURICLE TO FEMORAL AND BRACHIOCEPHALIC ARTERIES

WITH GRAVITY RETURN FROM LEFT AURICLE

MEAN PRESSURE (mm. Hg.) DATA, SHUNT FLOW AND SURVIVAL RESULTS FOR NINETY MINUTE AORTIC ARCH BYPASS

DOG NO.	MEAN PRESSURE IN PROXIMAL AORTA		MEAN PRESSURE CHANGE IN PROXIMAL AORTA	MEAN PRESSURE IN DISTAL AORTA		MEAN PRESSURE CHANGE IN DISTAL AORTA	MEAN PRESSURE IN CAROTID ARTERY		MEAN PRESSURE CHANGE IN CAROTID ARTERY	SHUNT FLOW cc./Kg./min.		SURVIVALS	COMPLICATIONS					Hgb. CONC. AT NINETY MINUTES mg.%
													NEURO.	UROLOGICAL				
	BEFORE BYPASS	DURING BYPASS		BEFORE BYPASS	DURING BYPASS		BEFORE BYPASS	DURING BYPASS		FEMORAL	BRACHIO-CEPHALIC			CONC. POWER (mosm./L.)		CREAT. CLEAR. (cc./min)		
														PRE-OP	POST-OP	PRE-OP	POST-OP	
27	100	120	+20	100	55	-45	100	80	-20	42	18	YES	normal	2000	2100	90	90	70
28	110	120	+20	110	70	-40	110	75	-35	42	18	NO	—	—	—	—	—	—
29	120	135	+15	120	60	-60	120	60	-60	42	18	YES	normal	2200	2400	80	90	65
30	110	140	+30	110	80	-30	110	65	-45	42	18	YES	normal	2400	2000	90	80	—
AVERAGE	110	131	+21	110	66	-44	110	70	-40									

Fig. 6.—*Aortic arch bypass employing a left auricle to femoral and brachiocephalic arteries shunt with gravity return from the left auricle.* This system is similar to that shown in Fig. 5 except that oxygenated blood is syphoned rather than pumped from the left auricle. At moderate flow rates it is possible to decompress the proximal aorta, adequately perfuse the distal visceral and cerebrum, and obtain a high rate of survival after 90-minute shuntings.

of perfusion under these circumstances. Both dogs showed no evidence of injury at the end of 1 week. Hemoglobin concentration in the plasma at the end of the 90-minute perfusions was approximately 70 mg. per cent.

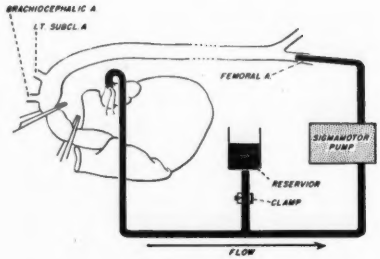
2. *Left auricle to femoral artery and brachiocephalic artery with gravity return from the left auricle:* This apparatus is shown in Fig. 6. With the apparatus used, the maximum flows obtainable ranged from 60 to 70 c.c./Kg./min. With gravity return when the ascending aorta is occluded, it is particularly important to have the catheter correctly positioned for adequate outflow; on occasion, cannulation of the mitral valve was necessary. Ninety-minute shuntings at the previously stated minimum flows of 60 c.c./Kg./min. were made in 4 dogs. Three dogs showed no evidence of injury at the end of 1 week. One dog died of hemothorax and massive atelectasis at 12 hours postoperatively.

Ascending Aortic Bypass.—

Two shunting arrangements were tested: (1) active pumping from the left auricle to the femoral artery with application of suction to the left auricle, and (2) gravity flow from the left auricle to a reservoir, thence pumping to the femoral artery.

1. *The left auricle to femoral artery shunt with pump return from the left auricle:* This apparatus is shown in Fig. 7. Once again the effect of varying flow rate on mean arterial pressure proximal and distal to the point of aortic occlusion was studied. It will be noted in Fig. 7 that, at a flow of 100 c.c./Kg./min., these two pressures were approximately equal and also approximated the aortic pressure before occlusion. A flow of about 60 c.c./Kg./min., which may be a reasonable minimum, resulted in a mean proximal pressure rise of 30 mm. Hg and a distal pressure fall of 50 mm. Hg, to a level of 70 mm. Hg. At flows below this level the distal pressure dropped to precariously low levels and the proximal pressure rose to dangerously high values. In all cases, at flows below 30 to 40 c.c./Kg./min. there was electrocardiographic evidence of severe left heart strain, and cardiac arrest or ventricular fibrillation almost always occurred within 5 minutes. At 60 c.c./Kg./min., transitory cardiac irregularities were again noted. At flows much in excess of 100 c.c./Kg./min. the demand of the pump exceeded the flow into the auricle and the tubing on the inflow side of the pump collapsed. Ninety-minute shuntings at the previously stated minimum flow rate of 60 c.c./Kg./min. were made and survival was attempted in 3 dogs. Two of the 3 dogs survived and were well at the end of 1 week. One died of unknown cause at 24 hours.

2. *Left auricle to femoral artery with gravity return from the auricle:* The apparatus is shown in Fig. 8. Actual flows obtainable by this system ranged from 60 to 70 c.c./Kg./min. in the 5 dogs run. Ninety-minute shuntings at the previously stated minimum flows of 60 c.c./Kg./min. were made and survival of the animals was attempted. Four of the 5 dogs survived and showed no evidence of injury at the end of 1 week. One dog died 6 hours postoperatively from massive atelectasis.



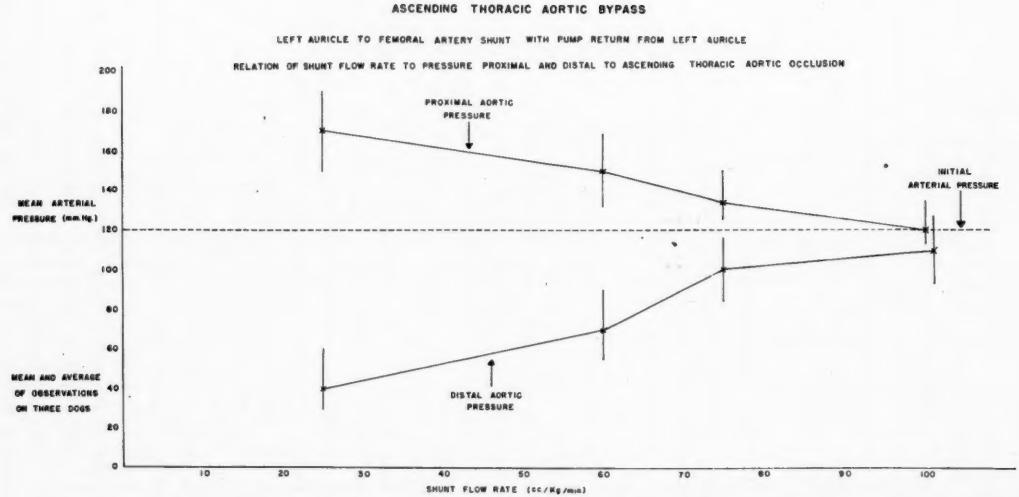
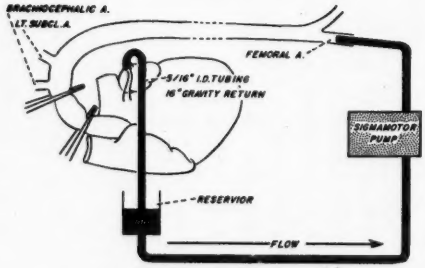


Fig. 7.—*Ascending thoracic aortic bypass employing a left auricle to femoral artery shunt with pump return from the left auricle.* By this system oxygenated blood is removed by active suction from the left auricle and via the femoral artery perfuses all aortic branches except the coronaries. The residual left auricular blood passes through the left ventricle and supplies the coronary vessels. It is possible to obtain physiologic flows and essentially normal pressures, proximal and distal to the aortic occlusion, by this method.



ASCENDING THORACIC AORTIC BYPASS

LEFT AURICLE TO FEMORAL ARTERY SHUNT WITH GRAVITY RETURN FROM LEFT AURICLE

MEAN PRESSURE (mm/Hg.) DATA, SHUNT FLOW AND SURVIVAL RESULTS FOR NINETY MINUTE ASCENDING THORACIC AORTIC BYPASS WITH AND WITHOUT CARDIAC ARREST

DOG NO.	MEAN PRESSURE IN PROX. AORTA BEFORE BYPASS	MEAN PRESSURE IN PROX. AORTA DURING BYPASS	MEAN PRESSURE CHANGE IN PROX. AORTA	MEAN PRESSURE IN DISTAL AORTA BEFORE BYPASS	MEAN PRESSURE IN DISTAL AORTA DURING BYPASS	MEAN PRESSURE CHANGE IN DISTAL AORTA	FLOW IN SHUNT cc/Kg/min.	SURVIVALS	COMPLICATIONS					HEMOGLOBIN CONC. AT NINETY MIN. mg.%
									NEUROLOGICAL	UROLOGICAL				
										CONG. POWER (mosm./L) PRE-OP	CONG. POWER (mosm./L) POST-OP	CREAT. CLEARANCE cc./min. PRE-OP	CREAT. CLEARANCE cc./min. POST-OP	
	WITHOUT CARDIAC ARREST													
26	120	145	+25	120	80	-40	60	NO	—	—	—	—	—	—
28	130	150	+20	130	60	-70	60	YES	normal	2000	1900	90	95	70
36	110	140	+30	110	55	-55	60	YES	normal	2300	2400	100	85	75
37	100	130	+30	100	75	-25	60	YES	normal	1800	2000	90	95	—
38	110	120	+10	110	60	-50	60	YES	normal	—	—	—	—	—
AVERAGE	114	137	+23	114	66	-48								
	WITH CARDIAC ARREST													
39	120	10	-110	120	80	-40	60	YES	normal	2200	2100	85	90	—
40	130	15	-115	130	70	-50	60	NO	—	—	—	—	—	—
41	130	15	-115	130	70	-60	60	NO	—	—	—	—	—	—
AVERAGE	127	13	-114	127	73	-50								

Fig. 8.—*Ascending thoracic aortic bypass employing a left auricle to femoral artery shunt with gravity return from the left auricle.* This system is similar to that shown in Fig. 7 but syphons rather than pumps blood from the left auricle. At moderate flow rates it is possible to decompress the proximal aorta, adequately perfuse the distal viscera, and obtain a high rate of survival after 90-minute shuntings. Even in the presence of cardiac arrest, passive flow of blood through the lungs provides sufficient blood for adequate flows.

In our investigation of the ascending aorta, an interesting phenomenon was noted. We could consistently clamp off the aorta up to approximately 2.5 cm. from the coronary ostia without any cardiac difficulty as long as appropriate flows were maintained, but occlusion closer than 2.5 cm. invariably caused cardiac arrest. Simultaneous pressure and electrocardiographic studies suggested that this phenomenon was due to myocardial ischemia.

The elastic reservoir in such a shortened aortic segment is too small to store during systole and deliver during diastole a sufficient volume of coronary flow. Heart action could be maintained by introducing additional blood into this segment from the pump, unless the clamp was so close to the heart as to occlude the coronary arteries. Three dogs were studied with the proximal clamp less than 2.5 cm. from the coronary ostia. Cardiac arrest occurred within 5 minutes in each case, but, in spite of arrest, after administration of transfusions to increase venous pressure, blood flow from the left auricle continued and was comparable in amount to that obtained without arrest. As shown in Fig. 8, these 3 dogs, which were perfused for 90 minutes at a flow of 60 c.c./Kg./min., had similar distal pressure studies as those obtained from the previous dogs which had normal cardiac action. Of course the proximal aortic pressure was low because of the absence of cardiac action. Two of these 3 dogs were readily resuscitated after the perfusion by removal of the clamp and defibrillation. One of the dogs was living and well at 1 week; the other died of a cardiac arrhythmia at 5 hours postoperatively. We were unable to resuscitate the heart of the third dog.

CASE REPORTS

The following pertinent clinical cases are reported and considered in the light of this animal work.

CASE 1.—C. J. (M.G.H.—Unit No. 108670) was a 60-year-old man who entered the hospital with a syphilitic thoracic aortic aneurysm, symptomatic for 10 years with recent onset of substernal pain radiating to the back. He had had a myocardial infarction 6 years prior to admission and had hypertension of 190/120 mm. Hg, but his heart was of normal size without evidence of valvular disease. According to an angiocardiogram, the aneurysm lay in the upper descending aorta just beyond the left subclavian artery.

At operation, the aneurysm was resected and replaced by an aortic homograft, using a left heart bypass from left auricle to femoral artery. Blood was taken via a gravity system from the left auricle through a tube, 0.8 cm. I.D., to a reservoir, thence pumped into the femoral artery through a No. 20 catheter.

The aneurysm ruptured during the procedure while it was being freed up prior to control of the aorta. The resultant massive hemorrhage and cardiac arrest were controlled by starting the bypass system and clamping the aorta proximal and distal to the lesion. The heart was readily resuscitated with intermittent compression and replacement of blood loss through the reservoir. Resection and graft required a left heart bypass of 1 hour and 20 minutes. During the first hour of bypass, the gravity return syphon was maintained at 18 inches and gave a perfusion flow of 1,500 c.c./min. (20 c.c./Kg./min.) and a proximal aortic pressure 30 mm. Hg above normal. During the last 20 minutes of perfusion, the gravity return syphon was increased to 25 inches with a resultant rise in perfusion flow to 2,250 c.c./min. (30 c.c./Kg./min.) and a resultant decrease in proximal pressure to only

14 mm. Hg above normal. As can be seen in Fig. 9, for an inflow tube, 0.8 cm. I.D., the above pressure differentials and resultant flows could be predicted from our previous in vitro data.

Postoperatively, the patient had a moderately severe oliguria for 3 days, but was eventually discharged without evidence of renal or neurological deficit and was well when last seen 9 months after operation.

Comment: The tubing size and original height of syphon in this case limited shunt flow to marginally adequate levels, resulting in elevation of the proximal aortic pressure during operation and temporary postoperative renal dysfunction.

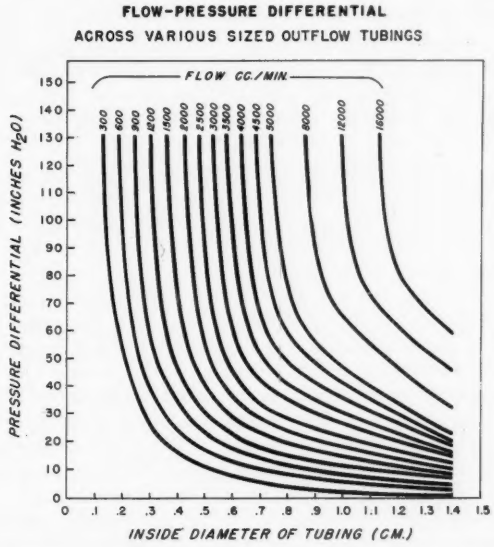


Fig. 9.—*Flow-pressure differential relationship of various-sized outflow catheters.* The amount of pressure differential across various-sized outflow catheters (12 inches in length) necessary to obtain a given flow is inversely proportional to the square of the inside diameter of the catheter.

It would have been desirable to have either larger tubing from the left auricle, or, as was eventually done, a stronger suction to provide a larger shunt.

The availability of reservoir prime in the bypass system, and suction apparatus to return blood from the operative field to the system readily solved an otherwise irretrievable situation with rupture of the aneurysm.

CASE 2.—J. F. (M.G.H.—Unit No. 1002417), a 63-year-old known hypertensive man with a previous history of myocardial infarction, entered the hospital with acute pain in the interscapular and substernal regions radiating down the left arm. Thirty hours after admission a diagnosis of dissecting aneurysm was made on the basis of x-ray findings and the sudden development of paraplegia.

At surgery, fenestration of the aneurysm in the descending aorta was performed, using a simple shunt from the left subclavian to the femoral artery with No. 18 catheters to bypass the occluded segment of descending aorta. The aorta was occluded for 40 minutes. Distal arterial pressures were not measured but could be expected to be low since the proximal

aortic pressure was not well decompressed by the shunt alone, and required administration of Arfonad during occlusion to keep it near pre-occlusion levels. There was severe oliguria for 4 days after operation (with good recovery of renal function and slight recovery from paraplegia at the time of discharge, 60 days after operation).

Comment: The simplicity of a simple shunt argues in its favor, but again flows to the lower body were hardly adequate as evidenced by the postoperative depression of renal function.

Because of the narrow caliber of the arterial catheters, required flows will be limited and the pressure differential between the two systems will be high. The interposition of a pump in such a shunt will improve flow and lower proximal arterial pressure as shown by the animal experiments.

CASE 3.—A. P. (M.G.H.—Unit No. 917634), a 64-year-old man, had had a known symptomatic syphilitic ascending aortic aneurysm for 2½ years. During the week prior to admission there had been sudden increase in right anterior chest pain and an appreciable increase in the size of the aneurysm. He was in mild congestive failure at the time of admission.

At operation, the apparent recent increase in aneurysmal size was found to be due to rupture of the right lateral wall of the ascending aortic aneurysm. Open reconstructive aneurysmorrhaphy was performed, using a left heart bypass consisting of a two tube (0.8 cm. I.D.), 25-inch syphon from the left auricle to a reservoir from which blood was pumped into the femoral artery through a No. 20 catheter.

Twelve minutes were required for evacuation of thrombus from the aneurysm, mobilization of relatively healthy vessel wall, and the application of a long clamp to restore aortic continuity. During this period, the aorta was clamped about 1 cm. beyond the aortic valve and at the innominate artery, and cardiac action gradually weakened and finally ceased, due to interference with coronary circulation by the proximal clamp. When aortic continuity had been restored, the clamps were removed and the left heart bypass was continued over the next 18 minutes, during which time strong cardiac action gradually returned.

A flow rate of approximately 4,000 c.c./min. (60 c.c./Kg./min.) with a resulting mean distal arterial pressure of from 80 to 90 mm. Hg was maintained during bypass, both before and during cardiac arrest. This is consistent with the experimental data shown in Fig. 9 for two tubings, 0.8 cm. I.D., with a 25-inch pressure differential. Postoperatively, the patient had a mild and transient oliguria for the first 24 hours without evidence of serious renal injury. His course was complicated by the development of auricular fibrillation and congestive failure. He also showed marked respiratory insufficiency attributable to the fact that both phrenic nerves had been cut during dissection of the aneurysm. He required the assistance of a respirator for 25 days. Thirty days after operation, the patient was ambulatory, breathing well, and asymptomatic when he suddenly died. Autopsy showed sepsis at the aortic suture line with resultant rupture and exsanguination.

Comment: The shunt flow of 60 c.c./Kg./min. past the obstructed ascending aorta provided adequate body perfusion in this case. Resistance to flow in the syphon tubing because of its greater size was considerably less than in Case 1, thus permitting the greater flow. Placement of the proximal aortic clamp too close to the coronary ostia resulted in cardiac arrest, but passive flow of blood through the lungs was sufficient to maintain perfusion and provide aortic pressure sufficient to resuscitate the heart.

CASE 4.—C. H. (M.G.H.—Unit No. 1008693), a 50-year-old man known to be hypertensive, was admitted with a dissecting aneurysm of the thoracic aorta of 40 hours' duration.

During the first few hours of hospitalization, he developed progressively severe symptoms of cardiac tamponade so an attempt to repair the primary tear in the ascending aorta was made. At operation, 400 c.c. of blood was released from the pericardium and a left auricle to femoral artery bypass was set up, using an inflow tube, 1.4 cm. I.D., with a 21-inch syphon from the left auricle. Blood was returned by a Sigmamotor pump through a No. 20 catheter in the femoral artery. The aorta was clamped at the innominate artery, 2.5 cm. from the heart. A shunt flow of 4,500 c.c./min. (70 c.c./Kg./min.) was obtained which resulted in a mean distal arterial pressure of 100 mm. Hg as compared with a mean pressure before clamping of 150 mm. Hg. This flow is consistent with the experimental data shown in Fig. 9 for a 1.4 cm. I.D. tubing with 21-inch syphon pressure differential.

During the first 10 minutes of perfusion, an attempt was made to identify and repair the primary tear. This was abandoned when the aorta tore free from the heart just beyond the coronary orifices, proximal to the controlling clamp. With no effective coronary perfusion, cardiac action ceased. Nevertheless, body perfusion continued at the previous level, employing the left auricle to femoral artery shunt. While bleeding from the left ventricle was minimized by pressure on the outflow tract, an aortic homograft was obtained and sutured end-to-end to replace the ascending aorta. Following restoration of aortic continuity, the ventricle was observed to be fibrillating and electrical defibrillation was accomplished. The left heart bypass was continued in parallel with the patient's own heart for about 5 minutes, following which time the shunt was discontinued and the patient was able to maintain a blood pressure at 140/80 mm. Hg. A shunt flow of 70 c.c./Kg./min. was maintained throughout the 1½ hour bypass, the blood moving passively through the lungs during the 1 hour and 20 minutes of cardiac arrest.

Postoperative electrocardiogram was unchanged from that observed preoperatively. Vital signs were well maintained and the patient had recovered consciousness when, about 4 hours after operation in the recovery room, there was a rush of blood from the left chest drainage tube and the patient died. Autopsy permission was not obtained.

Comment: The left heart bypass was adequate in this case requiring prolonged ascending aortic occlusion. Flows sufficient to maintain a satisfactory arterial pressure could be obtained with a syphon of adequate caliber and height from the left auricle. However, a pump return system would have been simpler and would have avoided the inconvenience of a large inflow tube and syphon gradient. Even with cardiac arrest, this system maintained adequate perfusion flow and pressures.

DISCUSSION

Left heart bypass offers a relatively simple means of compensating for thoracic aortic occlusion. Since no oxygenator is necessary, the required tubing and fittings can be stored sterile and assembled for prompt use in the operating room. The apparatus requires less than 500 c.c. of blood or saline for priming, minimizes the problem of air embolization, and avoids the current uncertainties of a pump-oxygenator in long perfusion. With its reservoir, this system gives an excellent safeguard against massive hemorrhage and enables immediate transfusion or autotransfusion.

This type of bypass can be employed in any of the three thoracic areas—ascending aorta, arch, or descending thoracic aorta. When correct shunt flows are maintained, it is possible to perfuse distal structures adequately and to avoid proximal hypertension and left heart strain. Proximal hypertension and cardiac arrhythmias become a problem and spinal cord and renal damage

may occur when flows are too low. Unnecessarily high flows will only put an added burden on the pumping apparatus and increase blood element damage.

For lesions involving only the descending thoracic aorta, either the left auricle or the subclavian artery is an equally good source of blood for shunting. The source most readily available in the operative field should be used. If the left auricle is used, either active pumping or gravity return from the left auricle can be employed. In order to obtain adequate flow with gravity, a large catheter must be used and an adequate syphon assured (Fig. 9). Pump suction allows the use of a smaller auricular catheter and eliminates concern about the height of the syphon. If the subclavian artery inflow system is employed it is almost mandatory to use a pumping system for long occlusions because a simple shunt with small easily insertable catheters is unable to transmit more than marginal flows.

For shunts past lesions of the ascending aorta or aortic arch, the left auricle is the only logical source of inflow blood. Here again, either active pumping or gravity return can theoretically be employed, but the increased flow requirement emphasizes the advantages of the pump return (Fig. 9). The dangers of inadequate flow are most apparent in ascending aortic occlusion, where low flows will result in severe proximal hypertension, left heart strain, and cardiac difficulties.

When occlusion occurs very close to the aortic valve, cardiac arrest may occur from insufficient coronary perfusion. This may result either from occlusion of the coronary ostia or as a result of there being inadequate systolic blood volume in the proximal aortic segment to fill the vessels during diastole. This difficulty was overcome here, as by Johnson,[9] by introducing blood from the pump into the proximal aortic segment.[9] As shown in dog experiments[10] and demonstrated in Case 9, even where cardiac arrest has occurred, the pressure of peripheral venous blood, when elevated by transfusion, circulates sufficient blood through the lungs and the left auricle to allow adequate pump flows with resultant satisfactory distal perfusion flow and pressure for periods of time up to 1 hour. Such an arrangement imposes the temporal limitations of ischemic cardiac arrest, and prolonged procedures would require cardiac cooling or some method of coronary perfusion.

CONCLUSIONS

1. Simple shunting around the occluded segment using a pump but not employing an oxygenator promises to be a feasible method of handling aneurysms in all areas of the thoracic aorta. (a) A simple circuit consisting of a pump from the auricle to the distal arterial tree with a reservoir attached to the intake line allows the most satisfactory control of flow rates and pressures. (b) In the case of the descending aorta, the subclavian artery can be substituted for the left auricle as a source of oxygenated blood, but adequate control of flow rate still requires a pump return system.

2. By simple regulations, the shunt flow and pressure in all areas can be controlled. Normal pressures and flows, both proximal and distal to the area

of occlusion, can be obtained but considerably less than normal pressures and flows are acceptable and compatible with recovery. In the dog, ideal and minimal acceptable flow rates at the various levels of aortic obstruction are shown in Table I.

TABLE I

	IDEAL (C.C./KG./MIN.)	MINIMAL ACCEPTABLE (C.C./KG./MIN.)
Descending aorta	75	30
Aortic arch		
Distal aorta	70 to 75	45
Thoracocervical trunk	20 to 25	15
Ascending aorta	100	60

Survival studies employing minimal acceptable flow rates at these three levels are shown in Table II.

TABLE II. SURVIVAL RESULTS OF 90-MINUTE SHUNTINGS AROUND ISOLATED SEGMENTS OF THORACIC AORTA

AREA	NO. OF DOGS	SURVIVALS	% SURVIVALS
Descending thoracic aorta	17	15	88
Aortic arch	6	5	83
Ascending thoracic aorta	11	7	64

3. Even in the face of cardiac arrest, these shunting systems can, as a temporary expedient, provide adequate flow and pressure during occlusion of the ascending aorta or aortic arch.

SUMMARY

In dealing with aneurysms or acute lesions of the thoracic aorta, it is necessary to shunt blood past any temporarily occluded segment, in order to perfuse the distal structures as well as to avoid proximal hypertension and left heart strain.

Temporary occlusion with bypass of the ascending aorta, the aortic arch, and the descending aorta were considered separately in these dog experiments. Various shunting arrangements were tried for each level of occlusion and the method most applicable for clinical use determined. For each shunting arrangement, measurement of flow rates and their relationship to proximal and distal pressure was accomplished. Optimal and minimally acceptable flow rates were determined by pressure studies and by animal survival of 90-minute occlusions of the thoracic aorta without central nervous system or visceral injury. Pertinent clinical cases are presented and discussed.

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REPAIR OF MITRAL INSUFFICIENCY DUE TO RUPTURED CHORDAE TENDINEAE

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THAT insufficiency of the mitral valve is correctable by open heart surgery has been amply demonstrated. The surgical technique has been based on the assumption that pure mitral insufficiency is the result of an absolute or relative deficiency of valve leaflet tissue in relation to the size of the mitral orifice. Thus, surgical correction has been accomplished either by narrowing the mitral annulus or by replacing deficient valvular tissue with immobile occluding prosthetic elements.[1-5] No different specific technique has been described for the correction of mitral insufficiency in the circumstance where it results from rupture of the chordae tendineae. The purpose of this communication is to illustrate a technique for the repair of such lesions and point out that, in certain instances, reconstruction of a competent mitral valve can be accomplished without mitral annuloplasty and without the use of prosthetic materials.

The chordae tendineae are crucially important to the normal function of the mitral valve, for they prevent eversion of its leaflets into the left atrium during ventricular systole.[6] Rupture of one or more chordae tendineae is occasionally the mechanism whereby mitral insufficiency results from rheumatic or bacterial endocarditis and also may result from external trauma.[7]

SURGICAL TECHNIQUE

Access to the operative area is achieved by right anterolateral thoracotomy in the bed of the intact sixth rib. Extracorporeal circulation[8] is instituted after cannulation of the venae cavae via the right atrial appendage and of the right external iliac or common femoral artery. The left atrium is widely incised just posterior to the interatrial sulcus. A sucker is inserted into the heart and the large amount of central blood is withdrawn. Just enough blood is left in the heart to cover the mitral orifice. Cardiac asystole is not instituted, because ventricular action is required so that the surgeon can assess the function of the valve and ascertain the area from which regurgitation originates. Thus, any systolic eversion of a portion of leaflet devoid of chordal attachment can be detected, as well as the regurgitant jet originating at the same area (Fig. 1, *a*).

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After an estimate has been made of the length of the flailing segment, the intracardiac sucker is passed well into the left ventricle and enough blood is withdrawn so that the mitral valve is clearly visible. The severed chorda and adjacent margin of the leaflet are grasped with forceps. A 3-0 silk suture is passed through the margin at one end of this untethered segment of leaflet, and the same suture is passed through the margin of the leaflet at the opposite end of this segment (Fig. 1, *b*). The two ends of this suture are then tied down over the redundant intervening leaflet tissue and the ruptured chorda

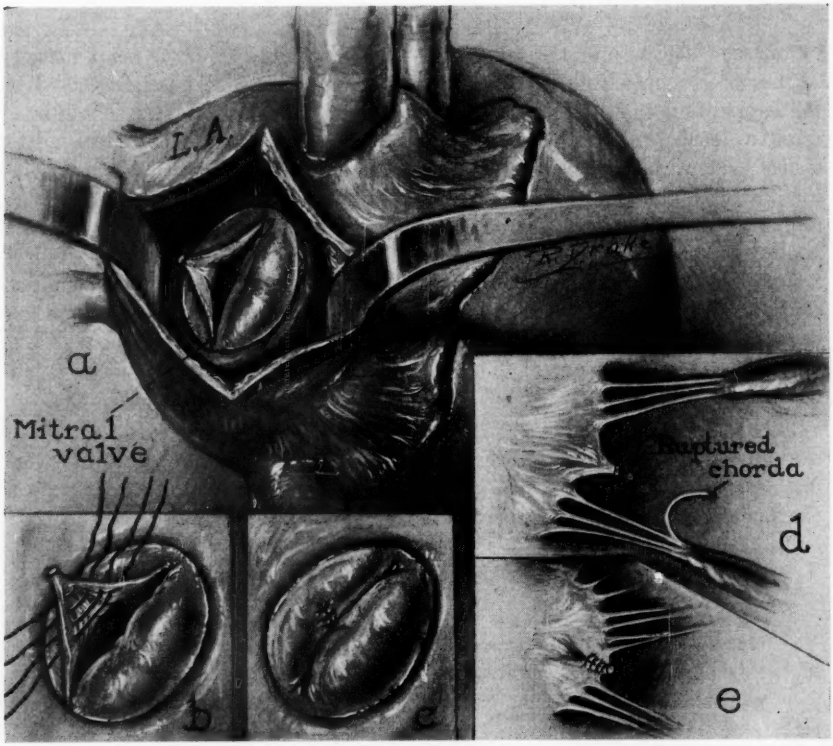

Fig. 1.—Technique of mitral valvuloplasty for repair of a ruptured chorda tendinea. *a*, The exposure of the mitral valve, illustrating a ruptured chorda tendinea. *b*, The placement of sutures to pleat the untethered segment. *c*, Valvuloplasty completed. *d*, Rupture of a chorda tendinea causes a corresponding segment of valve leaflet to be untethered or "flail." *e*, By shortening the flail segment, the remaining intact chordae can prevent eversion of the margin of the entire leaflet during ventricular systole.

to make a pleat in the redundant segment (Fig. 1, *c*). This segment is thereby shortened, with the result that the remaining intact chordae hold the entire leaflet taut during ventricular systole and eliminate overshooting and incompetence (Fig. 1, *d* and *e*). Several further interrupted sutures are placed to secure the pleat between the free margin of the leaflet and its base. The valve leaflets have been found to be slightly thickened and leathery, and therefore the sutures should hold securely.

When the leaflet has been sutured, the sucker is removed from the left ventricle and the blood level permitted to rise to and above the mitral valve. Then function of the valve is re-evaluated. When satisfactory competence of the valve is established, the left atrium and ventricle are allowed to refill with blood as the atriotomy is being repaired. Thus all air is expelled from the heart. Extracorporeal circulation is then terminated.

CASE REPORTS

CASE 1.—A 53-year-old white laborer had had rheumatic fever as a child and had known of a heart murmur for many years, but significant disability had begun only 6 months before he consulted the Mayo Clinic concerning this difficulty. Sharp, shooting, precordial pain had developed suddenly and was followed by rapid heart action, breathlessness on mild exertion, and orthopnea. He had not worked since that time.

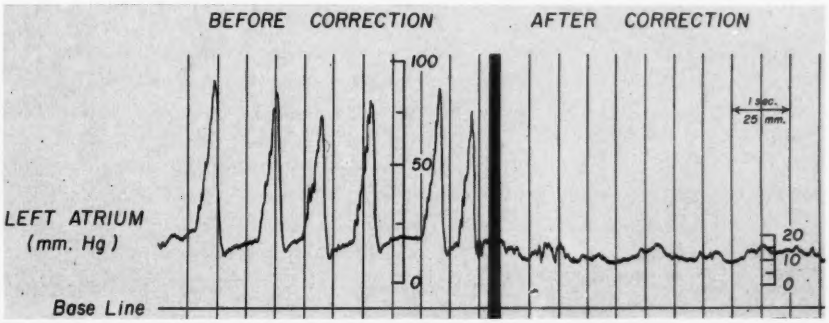

Fig. 2.—(Case 1.) Left atrial pressure during operation before and after correction of mitral insufficiency. Only mitral valvuloplasty for the correction of a ruptured chorda tendinea was required to achieve this striking correction of mitral insufficiency.

On examination, the classic signs of severe mitral insufficiency were noted. The systolic murmur was well transmitted to the base of the heart, the axilla, and the back. There was no evidence of calcification of the valve.

A diagnosis of severe isolated mitral insufficiency was made, probably on the basis of a ruptured chorda tendinea of the posterior mitral leaflet.[9] Open repair of the valve was carried out on Oct. 11, 1958, by the technique described. The only valvular abnormality encountered was a ruptured chorda tendinea of the posterior or mural valve leaflet, and this lesion alone required repair. No further procedures were carried out on the valve or valvular ring.

The postoperative recovery was satisfactory, and the patient was dismissed from the hospital on the ninth postoperative day.

A soft, Grade 2, systolic murmur, localized to the cardiac apex and unassociated with a thrill, was noted at each postoperative examination. Since dismissal, the patient has been working steadily and is unaware of any physical limitations except on severe exercise.

The peak pressure in the left atrium was found at operation to be approximately 85 mm. Hg before repair, but it fell to approximately 14 mm. Hg after repair (Fig. 2).

CASE 2.—A 27-year-old farmer had had scarlet fever as a boy, followed by a heart murmur and repeated bouts of rheumatic fever. At age 23, bacterial endocarditis developed, and hemolytic streptococci were cultured from the blood. Later, an embolic occlusion of the right external iliac artery occurred but caused no significant disability. Six months before he registered at the clinic, breathlessness on moderate exertion had developed, and paroxysmal nocturnal dyspnea had appeared.

Examination revealed the classic signs of severe mitral insufficiency, and the systolic murmur was well transmitted to the base of the heart and to the back. There was no evidence of valvular calcification. At cardiac catheterization a few days before operation, the pulmonary-artery wedge pressure (Fig. 3) was elevated. This is characteristic of predominant mitral insufficiency. Indicator-dilution curves demonstrated considerable prolongation of the disappearance slope, a finding that also is consistent with a diagnosis of mitral insufficiency (Fig. 3).[10]

A clinical diagnosis was made of mitral insufficiency, due either to a ruptured chorda tendinea or to perforation of a valve leaflet. Repair of the mitral insufficiency was carried out on Jan. 14, 1959.

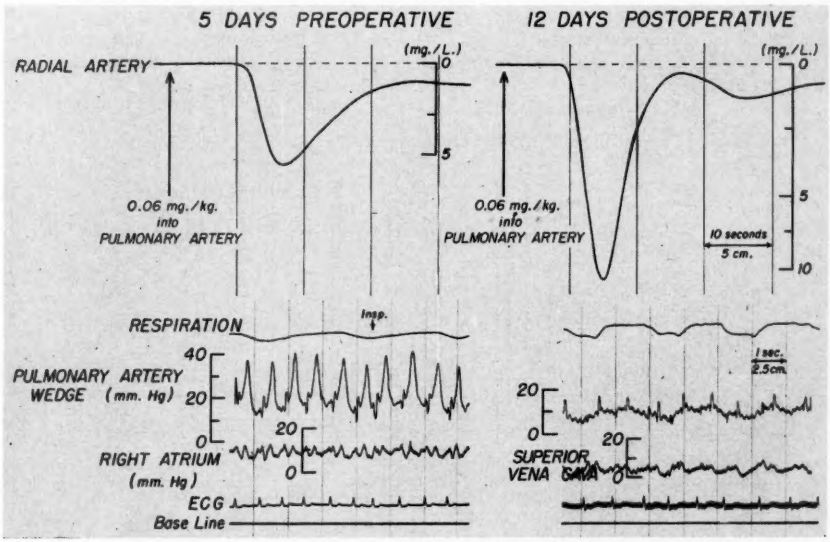

Fig. 3.—(Case 2.) Findings at cardiac catheterization before and after operation. The patient weighed 81 kilograms. Bacterial endocarditis had resulted in rupture of a chorda of the anterior mitral leaflet and a cleft in the posterior leaflet. Repair of the leaflets themselves was all that was required to correct mitral insufficiency.

Operation disclosed that previous bacterial endocarditis had resulted in rupture of a chorda which should normally have been attached to the lateral end of the anterior or aortic leaflet of the mitral valve. A small nodule of calcium on the free margin of the leaflet marked the site of the previous attachment of that chorda. The overshooting of this segment of leaflet was eliminated by the technique described. Exactly opposite this lesion was a wedge-shaped erosion or cleft in the posterior leaflet, and this was repaired by approximating the margins of the cleft with several interrupted sutures of 3-0 silk. When the repair was tested, some distortion of the leaflets was noted which caused gaping and incompetence at the medial commissure. Two sutures were placed in the margins of the adjacent leaflets to achieve partial fusion of this commissure. No further regurgitation through the valve was apparent after this procedure. No sutures were placed in the mitral annulus, and no prosthesis was employed.

Postoperative recovery was uneventful, and the patient was dismissed on the twelfth postoperative day. After operation, a Grade 1 to 2 systolic murmur which was well localized to the apex was present. The heart was quiet, and the patient has remained free of significant cardiac disability.

A peak pressure in the left atrium of 45 to 50 mm. Hg was demonstrated at operation before repair, and this was reduced to 16 mm. Hg after repair. Postoperative cardiac catheterization on the eleventh postoperative day revealed a pulmonary-artery wedge pressure of 11 mm. Hg, with a mean pressure of 7 mm. Hg. Indicator-dilution curves following repair were within normal limits (Fig. 3).

COMMENT

Mitral annuloplasty and leaflet substitution by an immobile prosthesis have been employed singly and in combination by those performing open heart surgery for mitral insufficiency.[1-5] This has been true even if one or more ruptured chordae tendineae have been identified as the basic cause of mitral insufficiency. Neither of these procedures seems as anatomically or functionally ideal as does reconstruction of the leaflet proper. The experience reported here demonstrates that, at least in certain instances, repair of the leaflets alone is sufficient to restore valve competence.

It must be stressed, therefore, that the valve leaflets should be carefully observed at the time of operation in the hope that correction of leaflet deformity and function might be accomplished in preference to mitral annuloplasty and replacement of the valve leaflet. When a ruptured chorda tendinea is identified as a cause for mitral insufficiency, the technique described for the repair of this defect should be carried out initially. That mitral insufficiency begets further mitral insufficiency seems clearly established[6] and is due to the fact that progressive dilatation of the mitral annulus may accompany the left ventricular dilatation which results from mitral incompetence. Therefore, although it was not necessary to combine repair of the leaflet with other types of procedures for correction of mitral insufficiency in the 2 cases presented, it seems reasonable to believe that mitral annuloplasty in combination with mitral valvuloplasty may be advantageous in certain instances.

The left atrial pressure tracing before and after valvuloplasty (see Fig. 2) strikingly illustrates the fact that function of the valve can be restored by reconstruction of the leaflet alone. The peak pressure of 85 mm. Hg in the left atrium recorded in Fig. 2 is believed to be the highest left atrial pressure reported and is in sharp contrast to the normal appearance of the tracing after valvuloplasty.

The 2 patients whose cases are reported have not been followed for a sufficient time to permit evaluation of the long-term result of mitral valvuloplasty or to answer the question definitively as to whether these sutured leaflets will heal securely. The critical period for possible dehiscence of these repairs probably has passed, however.

SUMMARY

The data presented indicate that mitral insufficiency can be corrected in certain instances by repair of the leaflets of the valve rather than by mitral annuloplasty or replacement of a leaflet with a prosthesis. When mitral insufficiency is due to rupture of one or more chordae tendineae, it may be repaired

by a technique which eliminates the overshooting of the untethered segment of leaflet. This procedure should be carried out as the first step in the correction of this type of mitral insufficiency. The leaflets of the mitral valve must be carefully scrutinized at the time of operation to determine whether or not reconstruction of the leaflet is possible. When it is, this is believed to be preferable to either mitral annuloplasty or replacement of the leaflet by an immobile prosthesis. In certain instances, it is likely that reconstruction of a leaflet and mitral annuloplasty may be beneficially combined.

The 2 patients for whom mitral valvuloplasty alone has been employed for the correction of mitral insufficiency have obtained excellent early results.

ADDENDUM

Recent examination 8 months after operation in Case 1 and a progress report from the other patient indicate maintenance of the initial benefit. In Case 1, the roentgenograms made on the return visit showed striking regression in size of the heart to normal and absence of pulmonary vascular congestion. Both patients continue with full employment.

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THE POSTMORTEM EXTERNAL APPEARANCE OF CONGENITALLY MALFORMED HEARTS AS AN AID TO SURGICAL DIAGNOSIS

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LESS THAN TWO decades ago, the accurate diagnosis of congenital cardiac defects was seldom achieved. By utilizing information obtained from electrocardiography, angiocardiography, and cardiac catheterization studies, an exact clinical diagnosis can now often be rendered and a program for surgical correction planned. Despite these facilities available for preoperative evaluation of the patient with congenital cardiac disease, the surgeon is occasionally confronted at the operating table with an unsuspected anatomic condition of the heart, or one which defies an in situ diagnosis. Since this problem usually precludes effective surgical action, we decided to undertake a study of the heart designed to discover whether or not certain external features of the anatomy at autopsy can be related to specific defects.

By its very nature, a study based on the postmortem heart imposes certain limitations. The external anatomy of the fixed heart is not identical with that of the fresh heart. Likewise, the external anatomy of the heart as seen outside the body is not absolutely identical with that inside the body. And, of course, the external anatomy of the postmortem heart in situ is not identical with that seen at surgery. In spite of these limitations, this work was undertaken and we believe yielded some information useful to the surgeon.

MATERIALS AND METHODS

The autopsy material which provided the basis for this study was taken from the Pathology Department at The Children's Memorial Hospital and from the Congenital Heart Disease Research and Training Center of the Hektoen Institute. Two hundred and ninety-six hearts were selected for evaluation. Many additional hearts were reviewed, but because of shapes distorted by fixation and previous study, they were not used in this work. It must be emphasized that only children's hearts were studied here.

The terminology used is adapted from the classification of congenitally malformed hearts previously presented by one of us (M. L.).[1, 2] Terms used in

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referring to borders, diameters, and certain other external parts of the heart are presented in Fig. 1.

Twenty-two complexes of congenital cardiac disease seen in Table I were studied. Several entities contained in the over-all classification were not considered for this study either because sufficient material was not available, or the condition is one which, at present, is not a diagnostic problem to the cardiac surgeon in the operating room. These are patent ductus arteriosus, vascular rings, adult-type coaretation of the aorta, aortic septal defect, complete transposition with cor biatriatum triloculare, mixed levocardia, dextrocardia, isolated congenital mitral stenosis, and Ebstein's complex.

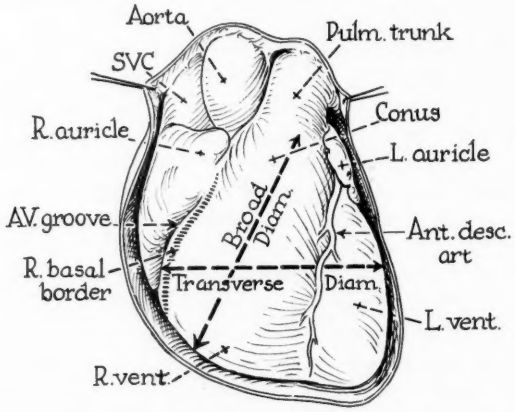

Fig. 1.—Diagrammatic sketch of the normal heart as seen from the anterior view, indicating various landmarks discussed in the text. Note (1) the broad and transverse diameters, (2) the right basal border of the right ventricle, (3) the conus of the right ventricle, and (4) the atrioventricular groove.

Each category of cardiac disease was studied separately. Five external features were chosen as criteria to be evaluated in each heart throughout all of the categories; namely, (1) the over-all shape or outline of the heart as seen anteriorly, (2) the position of the anterior descending coronary artery and its relationship to the formation of the apex of the heart, (3) the size and position of the arterial trunks at the base, (4) the shape of the right basal border of the right ventricle, and (5) the visibility of the left atrial appendage as seen anteriorly. These parts of the external anatomy of the heart are seen in their usual positions in the drawing of the normal heart in situ (Fig. 1).

In a few instances it has been possible to view the exposed heart at the beginning of an autopsy and to evaluate it externally. Such an evaluation has been especially helpful in the study since the distortions of the formalin-fixed specimen are absent.

OBSERVATIONS

The observations made in this study are embodied in the accompanying table. It can be noted that the over-all external features of some complexes aid

greatly in their diagnosis, while those of others are less helpful. Those in which they aid greatly are tetralogy of Fallot (Fig. 2), tricuspid atresia (Fig. 3), truncus communis (Fig. 4), fetal coarctation (Fig. 5), hypoplasia of the aortic tract complex (Fig. 5), and total anomalous pulmonary venous drainage (Fig. 6).

Tetralogy of Fallot (Fig. 2).—In the vast majority of instances in our series, the shape of the heart is either frankly boot shaped, or there is at least a blunting of the apex, giving it a snub-nosed appearance. The latter is obtained because the apex is formed by both the right and left ventricles, but, mainly, by the right. The anterior descending coronary artery forms a shallow S-shaped curve. The aorta is larger than the pulmonary artery and may or may not appear dextraposed. In some, the right basal border of the right ventricle is concave in its upper portion.

Tricuspid Atresia Without Transposition With Decreased Pulmonary Flow (Fig. 3).—The heart is, in most cases in our series, apple shaped. The apex is formed completely by the left ventricle with the anterior descending coronary artery pushed far over to the right. The aorta is larger than the pulmonary artery, in most cases the difference in size being very marked. The right atrioventricular groove usually is markedly accentuated, and there is a large bulging right atrial appendage.

Truncus Arteriosus Communis Persistens (Fig. 4).—The hearts in our collection are distinctly egg shaped with a marked increase in the transverse diameter. The anterior descending coronary artery originates more in the center of the base rather than on its left side, and as it descends to the apex, it is apparent that both ventricles help form the apex, the left perhaps more than the right. There is, of course, a single trunk emanating from the heart with no accessory band on its side.

Fetal Coarctation, Hypoplasia of the Aortic Tract Complex, and Total Anomalous Pulmonary Venous Drainage.—These hearts can be considered as a group because of their similar external appearance. The most important feature here is the marked displacement of the anterior descending coronary artery to the left and posteriorly so that it is barely seen anteriorly, or it is not seen at all (Figs. 5 and 6). Thus, the apex is formed exclusively by the right ventricle. There is an increase in the broad diameter because the complete anterior aspect of the heart is occupied by the right ventricle. The pulmonary artery is larger than the aorta. This feature is most marked in hypoplasia of the aortic tract complex (Fig. 5). Other external features also serve to distinguish between these complexes. In fetal coarctation* and hypoplasia of the aortic tract complex (Fig. 5), the anterior descending coronary artery is usually still seen anteriorly. This is not true of total anomalous pulmonary venous drainage (Fig. 6). The large right atrium and the increase in transverse diameter present in total anomalous pulmonary venous drainage further aid in distinguishing it

*The complex fetal coarctation is considered here in its pure form. This category does not include the transitional form of fetal coarctation in which the left ventricle is of considerable size.

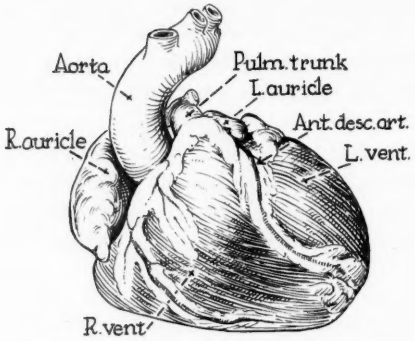

Fig. 2.—Diagrammatic sketch of tetralogy of Fallot as seen from the anterior view. Note (1) apex formed mainly by the right ventricle, (2) S-shaped anterior descending coronary artery, (3) concave right basal border, (4) snub-nosed apex, (5) small pulmonary trunk.

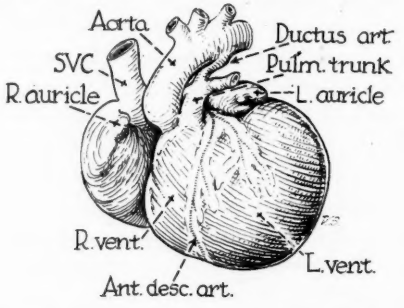

Fig. 3.—Diagrammatic sketch of tricuspid atresia without transposition with decreased pulmonary flow as seen from the anterior view. Note (1) apple-shaped heart, (2) anterior descending coronary artery displaced far to the right, (3) apex formed totally by the left ventricle, (4) deep atrioventricular groove, (5) large, bulging right atrium, (6) small pulmonary trunk.

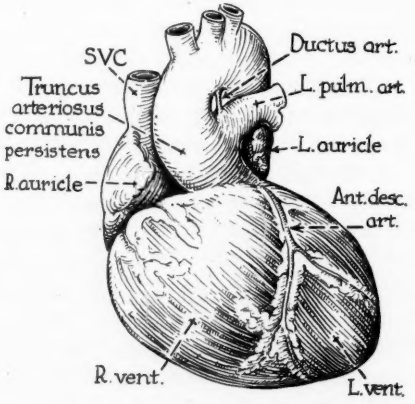

Fig. 4.—Diagrammatic sketch of common truncus as seen from the anterior view. Note (1) egg-shaped heart, (2) single trunk, (3) anterior descending coronary artery commencing more toward the center of the base of the heart.

from the other complexes. In addition, the left atrial appendage is always seen anteriorly in hypoplasia of the aortic tract complex, whereas it is not seen in total anomalous pulmonary venous drainage.

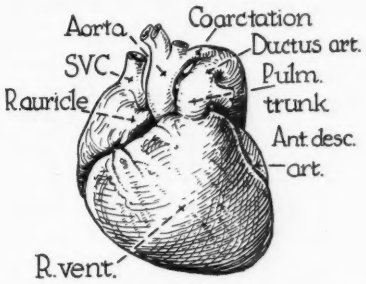

Fig. 5.—Diagrammatic sketch of fetal coarctation as seen from the anterior view. Note (1) anterior descending coronary artery displaced far to the left, (2) apex formed by the right ventricle, (3) ascending aorta small, but larger than the coarctated area, (4) marked increase in broad diameter.

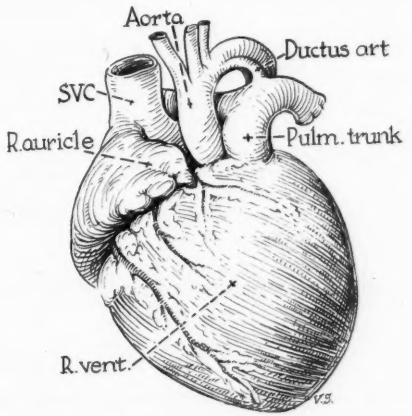

Fig. 6.—Diagrammatic sketch of total anomalous pulmonary venous drainage into the left innominate or the superior vena cava as seen from the anterior view. Note (1) anterior descending coronary artery not seen anteriorly, (2) very large right ventricle forming the apex, (3) marked increase in both broad and transverse diameters, (4) large, bulging right atrium, (5) large superior vena cava, (6) pulmonary trunk larger than the aorta.

DIFFERENTIATING FEATURES ACCORDING TO ISOLATED CRITERIA

As mentioned above, five criteria were evaluated in this work. Our findings pertinent to these criteria will now be considered.

1. *Anterior Descending Coronary Artery and Formation of the Apex.*—

If one uses this criterion in helping to evaluate the type of congenital heart disease, then the hearts in this series fall into five types: (a) Conditions in which the anterior descending artery is moved considerably to the right with the apex formed by the left ventricle. (b) Conditions in which the anterior descending artery is moved slightly to the right or is in normal position with the

TABLE I. TYPES OF PATHOLOGIC COMPLEXES STUDIED:

PATHOLOGIC COMPLEX	NO. OF HEARTS STUDIED	LOCATION OF ANTERIOR DESCENDING CORONARY ARTERY	APEX FORMATION	SHAPE OF HEART
1. Tetralogy of Fallot (Fig. 2)	46	Displaced to left, often S-shaped	Mainly by RV and septum with LV contributing to less extent	Roughly triangular or boot-shaped heart; apex snub-nosed
2. Partial transposition with pulmonary stenosis or atresia (pseudotruncus) (Fig. 13)	13	Displaced to left, more in atresia than in stenosis	Equally by both ventricles in stenosis; in atresia RV mainly forms apex	Increase in broad diameter
3. Taussig-Bing complex with pulmonary trunk mainly from right ventricle (Fig. 11)	5	In normal position	Totally by LV	Not remarkable
4. Taussig-Bing complex with pulmonary trunk mainly from left ventricle	12	In normal position	Totally by LV in some, and in others, RV contributes but LV predominates	Not remarkable
5. Complete transposition with normal architecture and without ventricular septal defect	24	In normal position or slightly to left	Usually equally by both vents; occasionally RV or LV may predominate	Not remarkable
6. Complete transposition with normal architecture and with ventricular septal defect (Fig. 8)	15	In normal position or slightly to left	Mainly by LV; occasionally both ventricles contribute equally	Not remarkable
7. Complete transposition with single ventricle and small outlet chamber (Fig. 15)	3	None identifiable	Single ventricle	Not remarkable
8. Complete transposition with ventricular septal defect and pulmonary stenosis	5	Displaced slightly to right	Totally by LV; occasionally RV contributes partially	Not remarkable
9. Truncus arteriosus communis persistens (common truncus) (Fig. 4)	4	Commences more in center of base than on left side	Both ventricles contribute equally or LV slightly more than RV	All hearts egg shaped with marked increase in transverse diameter
10. Tricuspid atresia without transposition with decreased pulmonary flow (Fig. 3)	20	Displaced far to right on anterior wall	Totally by LV	Apple shaped
11. Tricuspid stenosis with pulmonary stenosis or atresia	12	Displaced far to right on anterior wall	Usually totally by LV; occasionally RV contributes to less extent	Not remarkable

ANATOMIC PARTS EVALUATED AND FINDINGS

PULMONARY TRUNK AND AORTA AT BASE OF HEART	RIGHT BASAL BORDER OF RIGHT VENTRICLE	LEFT AURICLE	REMARKS
Aorta larger than PA; normal relative positions, or aorta anterior, and to right	Often concave	May or may not be seen anteriorly	Shape is not an index of pulmonary stenosis or atresia
Aorta larger than PA; normal positions, or aorta anteriorly and to right	Not characteristic	Usually seen	
Vessels side by side with aorta right and PA left, or aorta right and anteriorly and PA left and posteriorly; PA larger than aorta	Not characteristic	Usually seen	
As above, or directly anterior-posterior	Not characteristic	Seen in all hearts; displaced right atrial appendage in one case	
Aorta anteriorly and to right; PA posteriorly and to left; PA usually larger than aorta	Not characteristic	Usually seen	
Aorta anteriorly and to right; PA posteriorly and to left; PA usually larger than aorta	Not characteristic	Seen in all hearts	
Aorta anteriorly and slightly to left; PA posteriorly and slightly to right, or vessels anterior-posterior	Not characteristic	May or may not be seen	
PA and aorta in posterior-anterior position; aorta larger than PA	Not characteristic	May or may not be seen	
Single trunk	Not characteristic	Usually seen	
Aorta larger than PA; PA very small; normal relative positions	Not characteristic	Usually seen anteriorly	Right atrioventricular groove usually deepened; right atrial appendage large and bulging
Aorta larger than PA; normal relative positions	Not characteristic	Usually seen anteriorly	Atrioventricular groove not deepened; pulmonary trunk may be relatively large as compared to atresia

(Table I continued on next page)

TABLE 1.

PATHOLOGIC COMPLEX	NO. OF HEARTS STUDIED	LOCATION OF ANTERIOR DESCENDING CORONARY ARTERY	APEX FORMATION	SHAPE OF HEART
12. Left coronary artery from the pulmonary trunk	4	Slightly displaced to right	Totally by LV	Not remarkable
13. Isolated atrial septal defect—secundum type (Fig. 12)	12	Displaced to left	Both ventricles contribute equally in young hearts; in older hearts, mainly by RV or totally by RV	Prominent anterior bulge of conus
14. Isolated atrial septal defect—primum type	6	Displaced to left	Both ventricles contribute equally, or mainly by RV	About equal increase in both broad and transverse diameters, bulging conus
15. Isolated ventricular septal defect (Fig. 9)	37	Deviated slightly to right or left depending on dominant ventricle	Usually totally by LV; occasionally equally by both ventricles and infrequently mainly by RV	Conus bulge with increase in broad diameter
16. Hypoplasia of the aortic tract complex	6	Displaced far to left and posteriorly, barely seen anteriorly	Totally by RV	Triangular-shaped heart with marked increase in broad diameter
17. Fetal coarctation (Fig. 5)	21	Far to left	Totally by RV	Triangular-shaped heart with marked increase in broad diameter
18. Total anomalous pulmonary venous drainage (Fig. 6)	9	Displaced far to left and posteriorly, not seen anteriorly	Totally by RV	Marked increase in broad and transverse diameters, with conus bulge, anteriorly and superiorly
19. Common atrioventricular orifice (canal) (Fig. 10)	11	Displaced slightly to left, or in normal position	Totally or almost totally by LV	Triangular-shaped heart with increase in both broad and transverse diameters
20. Pure pulmonary stenosis (Fig. 14)	12	Displaced to left and is barely seen	Mainly by RV but LV also contributes; occasionally RV and LV contribute equally	Both broad and transverse diameters increased, but more in transverse
21. Aortic and subaortic stenosis (Fig. 7)	5	Displaced far to right	Totally by LV	Hypertensive shaped heart
22. Idiopathic hypertrophy with fibroelastosis	12	Displaced slightly to right	Usually totally by LV; occasionally RV contributes slightly	Heart roughly pear shaped

(Con'd)

PULMONARY TRUNK AND AORTA AT BASE OF HEART	RIGHT BASAL BORDER OF RIGHT VENTRICLE	LEFT AURICLE	REMARKS
Normal relative positions	Not characteristic	Not seen	
PA larger than aorta; normal relative positions	Not characteristic	May or may not be seen	
PA larger than aorta; normal relative positions	Not characteristic	May or may not be seen	
PA larger than aorta; normal relative positions	Rarely concave	May or may not be seen anteriorly	Apex mainly by RV when defect in posterior or apical part of ventricular septum
PA much larger than aorta; normal relative positions	Not characteristic	Seen in all hearts	Right ventricle makes up nearly all of the heart
PA larger than aorta; normal relative positions	Not characteristic	Usually seen	Disparity between pulmonary trunk and aorta; less than in hypoplasia of aortic tract complex
PA much larger than aorta	Not characteristic	Not seen	
PA larger than aorta; normal relative positions	Not characteristic	May or may not be seen	
PA about equal to aorta	Not characteristic; 2 cases concave with valvular and infundibular stenosis	Usually seen	
PA larger than aorta	Not characteristic	Usually seen	
PA about equal to aorta in size	Not characteristic	May or may not be seen	

apex formed by the left ventricle. (c) Conditions in which the anterior descending artery is moved slightly or moderately to the left with the apex formed by both ventricles. (d) Conditions in which the anterior descending artery is displaced markedly to the left and posteriorly so that it is barely visible or not seen at all anteriorly. (e) Conditions in which the anterior descending coronary artery is not recognized as such.

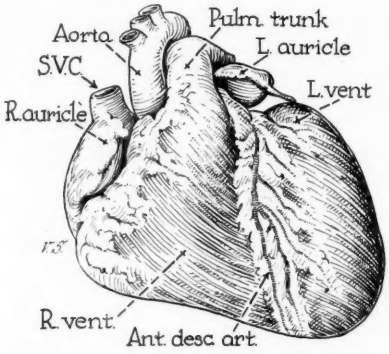

Fig. 7.—Diagrammatic sketch of aortic and subaortic stenosis as seen from the anterior view. Note (1) "hypertensive" shaped heart, (2) anterior descending coronary artery displaced far to the right, (3) large left ventricle forming the apex, (4) aorta smaller than the pulmonary trunk. Refer to Table I for variations.

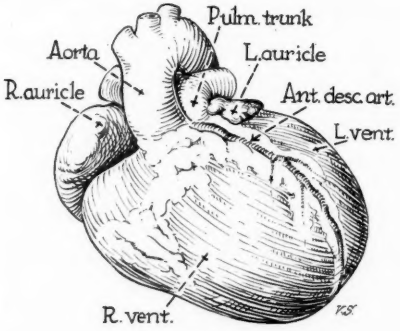

Fig. 8.—Diagrammatic sketch of complete transposition with normal architecture as seen from the anterior view. Note (1) aorta anterior and to the right, and pulmonary trunk posterior and to the left.

(a) Conditions in which the anterior descending artery is moved considerably to the right with the apex formed by the left ventricle. This occurs in tricuspid atresia (Fig. 3) and stenosis complexes, aortic and subaortic stenosis complexes (Fig. 7), and in origin of the left coronary artery from the pulmonary artery. The differentiating characteristics of tricuspid atresia and stenosis complexes are described previously. In aortic and subaortic stenosis, in the small series studied, the pulmonary artery was larger than the aorta. This is not true of aberrant origin of the coronary artery from the pulmonary artery.

(b) Conditions in which the anterior descending artery is moved slightly to the right or is in normal position with the apex formed by the left ventricle. This is seen in complete transposition with normal architecture (Fig. 8), with or without pulmonary stenosis, in the Taussig-Bing complex, and in idiopathic hypertrophy with fibroelastosis. It occurs in some instances of ventricular septal defect (Fig. 9) and common atrioventricular orifice (Fig. 10). Complete

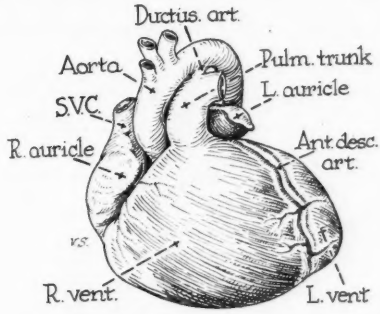

Fig. 9.—Diagrammatic sketch of one type of isolated ventricular septal defect as seen from the anterior view. Note (1) large right ventricle, (2) pulmonary trunk larger than the aorta, (3) anterior descending coronary artery displaced a little to the left, (4) apex formed by the left ventricle. Refer to Table I for variations.

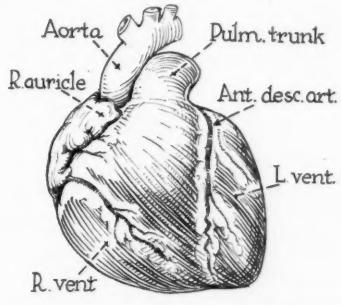

Fig. 10.—Diagrammatic sketch of isolated common atrioventricular orifice as seen from the anterior view. Note (1) apex formed by the left ventricle, (2) pulmonary trunk larger than the aorta. Refer to Table I for variations.

transposition and the Taussig-Bing heart (Fig. 11) may be differentiated from idiopathic hypertrophy by the abnormal position of arterial trunks. Ventricular septal defect cannot safely be differentiated from common atrioventricular orifice by external appearance alone.

(c) Conditions in which the anterior descending artery is moved slightly or moderately toward the left with the apex constituted by both ventricles. This is seen in atrial septal defect (Fig. 12), in some cases of ventricular septal defect and common atrioventricular orifice (Fig. 10), in tetralogy of Fallot (Fig. 2), in partial transposition with pulmonary stenosis (Fig. 13), in some cases of complete transposition with normal architecture (Fig. 8), and in pure pulmonary stenosis (Fig. 14). Tetralogy of Fallot is differentiated as previously

stated. Complete transposition is distinguished in this group by the positions of the arterial trunks, and the latter may also serve to differentiate those cases of partial transposition in which the abnormal position of vessels is seen externally. Partial transposition with pulmonary stenosis in which the position of arteries is normal externally may be differentiated from all types of isolated septal defects and pure pulmonary stenosis with large pulmonary artery by the

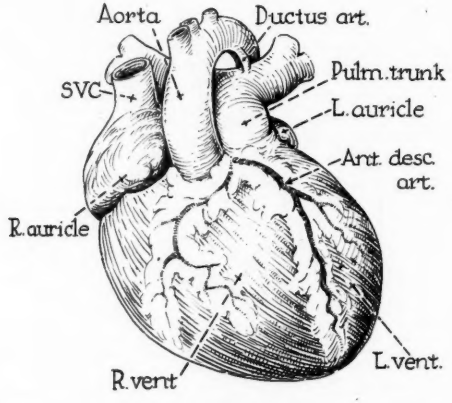

Fig. 11.—Diagrammatic sketch of Taussig-Bing complex as seen from the anterior view. Note (1) apex formed by the left or both ventricles, (2) aorta to the right and slightly anterior, and the pulmonary trunk to the left and slightly posterior, (3) pulmonary trunk considerably larger than the aorta.

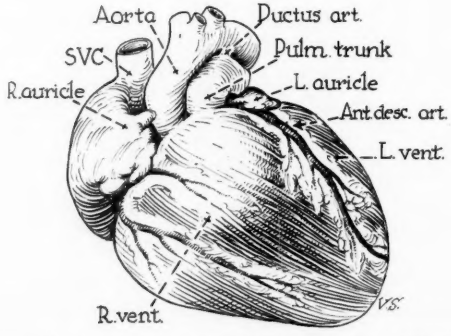

Fig. 12.—Diagrammatic sketch of atrial septal defect of the primum or secundum types as seen from the anterior view. Note (1) large, bulging right atrium, (2) apex formed completely or mainly by the right ventricle, (3) anterior descending coronary artery displaced to the left, (4) anterior bulge of the conus, (5) pulmonary trunk larger than the aorta. Refer to Table I for variations.

small size of the pulmonary artery in the partial transposition complex. When pure pulmonary stenosis has a small pulmonary artery it may perhaps be differentiated externally from partial transposition with normal position of arteries by the shape and size of the heart. In partial transposition with pulmonary stenosis the heart is in general not enlarged; that is, there is an increase

in the broad diameter but not in the transverse, while in pure pulmonary stenosis there is an increase in both diameters. It is possible to differentiate atrial septal defect (Fig. 12), ventricular septal defect (Fig. 9) and common atrioventricular orifice (Fig. 10) from pure pulmonary stenosis with large pulmonary artery (Fig. 14) in most cases by the considerable displacement of the anterior descending artery to the left in pure pulmonary stenosis so that it is just seen. It appears to be impossible from this study to differentiate all cases of atrial and ventricular septal defects and common atrioventricular orifice from each other.

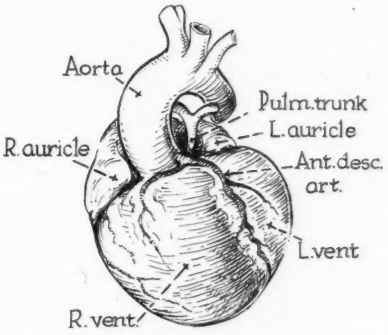

Fig. 13.—Diagrammatic sketch of partial transposition with pulmonary stenosis or atresia as seen from the anterior view. Note (1) anterior descending coronary artery displaced to the left with the apex formed mainly or completely by the right ventricle, (2) aorta anterior and to the right. Refer to Table I for variations.

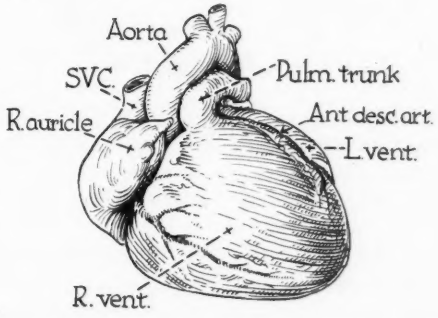

Fig. 14.—Diagrammatic sketch of pure pulmonary stenosis as seen from the anterior view. Note (1) anterior descending coronary artery displaced far to the left, but seen anteriorly, (2) apex formed by the right ventricle, (3) pulmonary trunk about the same size as the aorta. Refer to Table I for variations.

(d) Conditions in which the anterior descending artery is moved markedly to the left and posteriorly. The complexes included in this category are described above.

(e) Conditions in which the anterior descending artery is not identifiable as such. In the groups studied here only complete transposition with single ventricle and small outlet chamber has this characteristic (Fig. 15).

2. *Size and Position of the Arterial Trunks at the Base.—*

a. *Normal position:* (1) Aorta larger than the pulmonary artery. This is found in some cases of tetralogy of Fallot (Fig. 2), in tricuspid atresia and stenosis (Fig. 3), in some cases of partial transposition with pulmonary stenosis (Fig. 13), and in some instances of pure pulmonary stenosis (Fig. 14). Tricuspid atresia and stenosis and tetralogy have distinct external features previously described. Likewise, pure pulmonary stenosis with small pulmonary artery can be differentiated from partial transposition as described above.

(2) Pulmonary artery larger than aorta. This is seen in hypoplasia of the aortic tract complex (Fig. 5), total anomalous pulmonary venous drainage (Fig. 6), fetal coarctation, atrial septal defect (Fig. 12), ventricular septal defect (Fig. 9), and common atrioventricular canal (Fig. 10). As stated above, the former three can be differentiated, while the latter three cannot always be differentiated from each other.

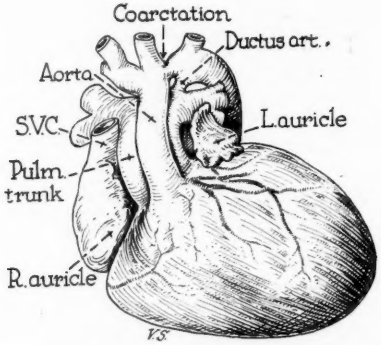

Fig. 15.—Diagrammatic sketch of complete transposition with single ventricle and small outlet chamber as seen from the anterior view. Note (1) the lack of a typical anterior descending coronary artery, (2) aorta and pulmonary trunk in anterior-posterior position. Refer to Table I for variations.

b. *Abnormal position of arterial trunks:* The aorta may be (1) slightly dextraposed and hence on the same lateral plane as the pulmonary, (2) the aorta may be anterior and to the right, and the pulmonary artery posterior and to the left, (3) the aorta may be anterior and the pulmonary artery posterior, (4) the aorta may be anterior and to the left, and the pulmonary artery posterior and to the right.

(1) Aorta slightly dextraposed. This is seen in some cases of tetralogy of Fallot and partial transposition (Fig. 13). The former have differentiating characteristics as described above, and were thus differentiated from the latter in this study.

(2) Aorta anterior and to the right, and the pulmonary artery posterior and to the left. This is seen in some cases of the Taussig-Bing heart (Fig. 11) and in complete transposition with normal architecture (Fig. 8). In both of these complexes, the pulmonary artery is larger than the aorta, and the two complexes cannot be differentiated externally.

(3) Aorta and pulmonary artery directly anterior and posterior. This is seen in complete transposition with normal architecture with pulmonary stenosis, in some cases of complete transposition with single ventricle and small outlet chamber, and in some cases of the Taussig-Bing heart. The former is easily differentiated from the latter two by the size of the pulmonary trunk.

(4) Aorta to the left and anterior, and pulmonary artery to the right and posterior. This is seen only in complete transposition with single ventricle and small outlet chamber in this series.

3. *Right Basal Border of the Right Ventricle.—*

The concave right basal border of the right ventricle occurs most frequently in tetralogy of Fallot in our series, but also was present in two hearts with ventricular septal defect and in one heart with pure pulmonary valvular and infundibular stenosis.

4. *Visibility of the Left Atrial Appendage From the Anterior View.—*

In two complexes in this study the left atrial appendage is never seen anteriorly. This is in total anomalous pulmonary venous drainage (Fig. 6), and in aberrant left coronary artery from the pulmonary artery. The left atrial appendage is always seen in this study in hypoplasia of the aortic tract complex (Fig. 5) and in complete transposition with normal architecture and ventricular septal defect (Fig. 8). In other conditions the left auricle is too variable to be contributory in differential diagnosis.

DISCUSSION

From our observations it is clear that the external morphology of the heart is a great aid in diagnosis in tetralogy of Fallot (Fig. 2), tricuspid atresia (Fig. 3), truncus communis (Fig. 4), fetal coarctation (Fig. 5), hypoplasia of the aortic tract complex, and total anomalous pulmonary venous drainage (Fig. 6). It is also evident that the position and size of the arterial trunks, and the course of the anterior descending coronary artery may be an aid to the diagnosis of a complex.

From the surgical point of view, it may be necessary to differentiate tetralogy of Fallot, partial transposition with pulmonary stenosis or atresia, truncus communis, and pure pulmonary stenosis. It may be possible to differentiate tetralogy of Fallot (Fig. 2) from partial transposition with pulmonary stenosis (Fig. 13) (double outlet right ventricle) in children. In tetralogy of Fallot, the concave proximal border of the right ventricle and the snub-nosed apex are characteristically present, while these are characteristically absent in the latter. The number of partial transpositions studied in this series, however, is too small to reach a more definite conclusion. Likewise, it may be possible to differentiate truncus communis from pseudotruncus. In this series, true truncus had a characteristic egg-shaped heart with the anterior descending artery starting in the middle of the base of the heart (Fig. 4). Pseudotruncus (partial transposition with pulmonary atresia) (Fig. 13) was not characterized in this way.

Here again, however, the number of hearts studied is insufficient for definitive evaluation. It may be possible to differentiate tetralogy and partial transposition from pure pulmonary stenosis. In the latter the anterior descending coronary artery is pushed far to the left, and there is an increase in transverse diameter. These characteristics are not usually seen in the former two.

In the field of complete transposition, it may be possible to differentiate some of the complexes from others by the position of the arterial trunks. In complete transposition with normal architecture (Fig. 8) and in some cases of the Taussig-Bing heart (Fig. 11), the aorta is situated anterior and to the right, and the pulmonary trunk posterior and to the left. In some cases of Taussig-Bing and in complete transposition with pulmonary stenosis, the aorta and pulmonary trunk are in a direct anterior-posterior position. Only in complete transposition with single ventricle (Fig. 15) in this study was the aorta situated anteriorly and to the left and the pulmonary trunk posterior and to the right. It is, of course, known that the latter arrangement may also be found in some cases of corrected transposition, and perhaps in complete transposition with cor biatriatum triloculare. (The latter two groups are not studied in this series.) Thus, the arrangement of the vessels may serve to differentiate complete transposition with normal architecture and Taussig-Bing on the one hand, from some cases of single ventricle with small outlet chamber and corrected transposition on the other hand.

It is unfortunately not possible from this study to differentiate clearly the various septal defects from external morphology alone. Atrial septal defect of the primum type is indistinguishable from atrial septal defect of the secundum type. Both show some difference, however, from most ventricular septal defects and common atrioventricular orifice. Thus, in this series, in most cases of ventricular septal defect and common atrioventricular orifice, the apex is formed mainly by the left ventricle. In children, however, in atrial septal defect, the apex is made up mainly by the right ventricle. When the apex is formed by both ventricles in atrial and ventricular septal defect, the large bulging right atrium seen in the former may help to differentiate it from the latter.

It must be re-emphasized that all our findings do not necessarily apply at the operating table. To become more valid, this type of study needs to be implemented with careful surgical observation.

CONCLUSION

1. A study of the external morphology of 296 autopsied congenital hearts was made with the purpose of seeing what helpful information could be obtained for the recognition of the nature of the complex.

2. The most helpful external features are (1) the shape of the heart, (2) the course of the anterior descending coronary artery and the composition of the apex, and (3) the size and position of the arterial trunks at the base.

3. The external morphology of the following complexes helps greatly in their recognition: (a) tetralogy of Fallot, (b) tricuspid atresia, (c) truncus communis, (d) total anomalous pulmonary venous drainage, and (e) fetal coarctation.

4. It is possible to differentiate by means of the external topography some subtypes of complete transposition from others.

5. It is not possible to differentiate absolutely from the external topography alone the various types of septal defects.

ADDENDUM

Since this paper was written, we have analyzed more than 50 more congenitally malformed hearts. These have revealed two changes from the above observations. In 1 case of total anomalous pulmonary venous drainage into the coronary sinus, the anterior descending coronary artery was still seen anteriorly as in fetal coarctation. In several cases of partial transposition with pulmonary stenosis, the shape of the heart resembled that of tetralogy of Fallot.

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PHYSIOLOGIC AND ANATOMIC STUDIES THIRTY-FIVE MONTHS AFTER SUCCESSFUL REPLANTATION OF THE LUNG

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INTRODUCTION

IN FEBRUARY, 1951, the first successful autologous lung replantation was reported by Juvenelle and his associates.[1] This report includes observations made 35 months after lung replantation in the original surviving animal. During this period, the dog was in good health.

The purpose of this experiment was to determine the long-term physiologic and anatomic status of such a replanted lung. Essentially, the operation done was right pneumonectomy and immediate replantation. Postoperatively, repeated fluoroscopy showed apparently normal ventilation. On this evidence, gross mechanical integrity of the right lung could be concluded.

The following physiologic aspects were studied: (1) the determination of the relative minute volume and oxygen uptake between the normal left lung and the replanted right lung, (2) the determination of the extent of renervation of the replanted lung, and (3) the evaluation of any change in the circulation to the lung.

METHODS AND RESULTS

1. Under intravenous barbiturate anesthesia, the main bronchi were intubated and connected to a bronchospirometer and recording kymograph. Determinations computed from the kymogram showed a minute ventilatory volume in the replanted lung of 40 per cent of the total. Oxygen uptake calculations indicated that the replanted lung accounted for 34 per cent of the total. These moderate diminutions from predicted values may reflect, in part at least, the effects of the primary surgical procedure.

2. The functional determination of the presence or absence of renervation in this preparation was limited to a study of the integrity of the *afferent* vagal fibers. This pathway carries the impulses which mediate the Hering-Breuer

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reflex. It is assumed that if regeneration of these fibers occurred, there would be an intact reflex arc on the right. In Fig. 1, the kymogram shows simultaneous recordings of ventilation from the left and right lungs. The first series shows normal ventilation for several cycles, followed by occlusion of the tube to the left main bronchus during inspiration. Because of the integrity of the afferent vagal fibers on the unoperated side, impulses reach the respiratory center and the left reflex arc is completed through the phrenic nerve to the diaphragm. Relaxation of the diaphragm occurs, resulting in expiration and temporary cessation of respiration. Because of other control of phrenic nerve function, escape occurs and respiration in the right lung again begins.

In the next series, the tube to the right main bronchus is occluded. There is no noticeable effect on the action of the diaphragm.

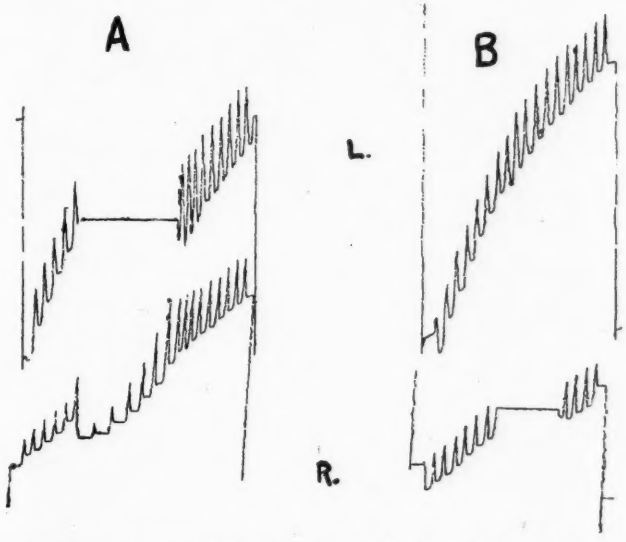

Fig. 1.—Spirogram of left lung (*above*) and right lung (*below*). In series *A*, occlusion of the left main bronchus results in temporary cessation of respiration followed by escape (Hering-Breuer reflex). In series *B*, occlusion of the right main bronchus does not result in cessation of left lung respiration.

From these records, we conclude that the Hering-Breuer reflex is absent on the operated side, presumably because of insufficient functional regeneration of afferent vagal fibers across the suture lines. No conclusions can be drawn from this experiment with regard to the presence or absence of regeneration of pre-ganglionic efferent vagal or post-ganglionic sympathetic pathways.

3. Evaluation of the pulmonary circulation was accomplished by angiocardiography (Fig. 2). These studies revealed a normal pulmonary arterial system with no apparent difference noted between the right and left sides.

Gross Examination.—

Shortly after the completion of the physiologic studies, the animal was sacrificed. Photographs were taken and multiple specimens from both lungs

were excised for histologic analysis. Examination of the in situ specimen revealed no apparent abnormality of the cardiopulmonary system, and all lines of anastomosis were smooth and well healed. On opening the heart, an old, organized, occluding thrombus was found in the superior pulmonary vein; this was probably an early postoperative event. There had been no clinical or radiographic evidence of massive venous congestion or infarction at any time in the postoperative period. The normal appearance of the operated lung at postmortem also ruled out these changes.

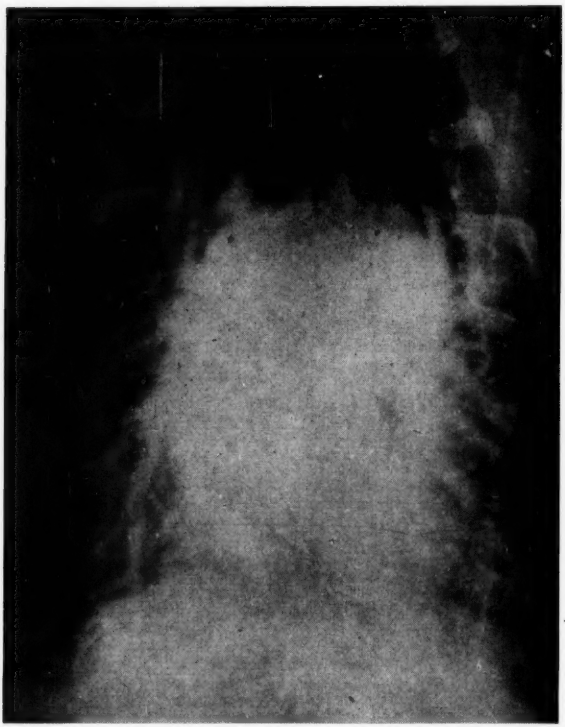

Fig. 2.—Angiocardiogram made 35 months after autotransplantation showing normal pulmonary circulation bilaterally.

Histologic Examination.—

Numerous comparable longitudinal and cross sections were taken from the main bronchi, pulmonary arteries and veins, and from more peripheral areas of both lungs. These were subjected to various histologic staining techniques and mounted for microscopic analysis. Silver impregnation was used on some sections to show the nerve tissue elements of the lung and pulmonary vessels.

The following observations were made.

Right main bronchus: The nerve fibers proximal and distal to the suture were not numerous. There was evidence of regeneration across the suture line.

Distal to the suture, numerous partially regenerated distal stump fascicles were seen. The axons were predominantly of small caliber, 1 to 2 μ; but some were of larger caliber, 4 to 5 μ. The latter were thought to be pre-ganglionic fibers. No ganglion cells were seen.

Right upper bronchus (Fig. 3): Numerous well-impregnated nerve bundles are present external to cartilage and are usually seen coursing along side arteries. Some fascicles appear to be incompletely filled with nerve fibers. A section through a portion of the middle lobe showed essentially the same pattern.

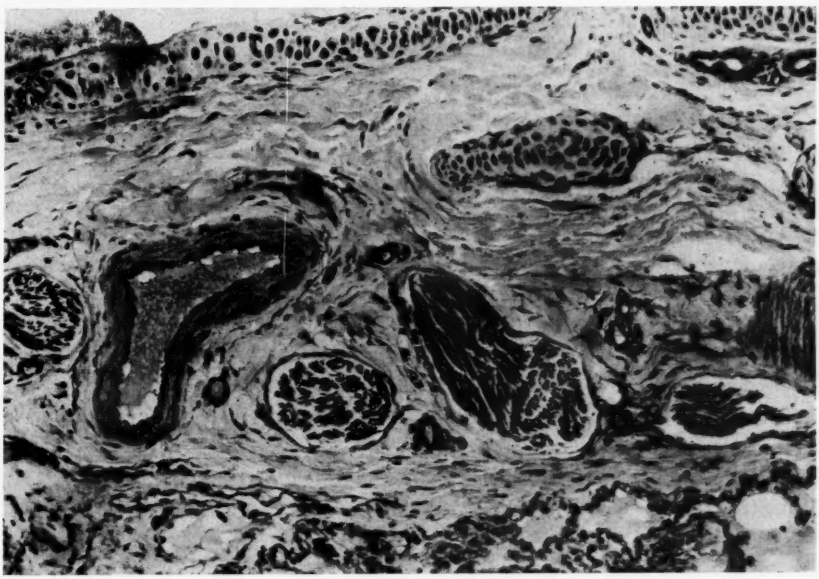

Fig. 3.—Photomicrograph of a section of the right main bronchus distal to the suture line. Note presence of peri-arterial nerve bundles with incomplete filling of some fascicles (×200; reduced ¼).

Right pulmonary artery: Nerve fibers could be seen crossing in the connective tissue across the suture line. Fibers were more numerous proximal to the suture line.

Comparative sections of pulmonary parenchyma of both sides showed no essential difference between the right and left lung.

DISCUSSION

Section of the main bronchus would transect pre-ganglionic vagal, afferent vagal, and post-ganglionic sympathetic fibers. It was concluded from analysis of slides that regeneration across the suture line had occurred. What percentage and what kind of fiber successfully regenerated is impossible to determine in this type of study. It was clear, however, that there were nearly as many

fibers coursing along the secondary and small bronchi on the side operated upon, as there were in the case of the normal left side. The absence of the Hering-Breuer reflex, however, indicates an absence of *functional* regeneration of afferent nerve fibers.

Functionally and anatomically, the denervated lung appeared not significantly different from the normal one after this time lapse. The moderate deficiency in oxygen uptake is consistent with the relative ventilation in this lung and is probably due to postoperative parietal restriction.

Examination of the serial radiographs from angiocardiography indicated no gross difference in rate or volume of blood flow in the denervated lung insofar as this interpretation can be made from dye distribution. In addition, the oxygen uptake paralleling the ventilation would suggest a normal pulmonary artery flow on this side.

SUMMARY

1. Anatomic and physiologic observations are reported in a dog which was sacrificed 35 months after successful autologous replantation of an excised lung.

2. Bronchospirometric studies revealed only moderate loss of pulmonary function in the replanted lung.

3. A loss of the Hering-Breuer reflex of the replanted lung was demonstrated and this was taken as representing failure of afferent vagal regeneration.

4. Examination of the cardiopulmonary system of the sacrificed dog revealed no gross abnormality, other than a thrombosed superior pulmonary vein on the side operated upon.

5. Microscopic study of the replanted lung showed regeneration of nerve elements across the suture line. The physioanatomic classification of the regenerated element could not be determined in this study. The histologic findings of the lung operated upon were otherwise normal.

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THE MANAGEMENT OF BRONCHOPLEURAL FISTULAS

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BRONCHOPLEURAL fistula is the most dreaded complication of pulmonary surgery. Although uncommon in nontuberculous pulmonary surgery, the incidence of bronchopleural fistula in resection for pulmonary tuberculosis varies widely in the current literature. The average incidence, from collected papers between 1951 and 1958, is 6.8 per cent.[1] In our own hands in 200 consecutive resections for pulmonary tuberculosis, 2 cases were complicated by fistula and 1 of these patients died in spite of active surgical management. Once a bronchopleural fistula occurs, a mortality rate of around 30 per cent[2] is common, irrespective of how it is managed. This complication is the commonest cause of postoperative morbidity and mortality and constitutes the greatest hazard in resection for pulmonary tuberculosis.

Because of the controversy in the literature about the management of bronchopleural fistulas, we felt that our experience in the management of 10 patients, 8 of whom were originally operated upon by other surgeons, is worthy of analysis. No attempt will be made to emphasize the etiology and diagnostic features nor the pathogenesis[3] since these have been well documented.

CASE REPORTS

CASE 1.—F. S., a 36-year-old woman, had had a right upper lobectomy for fibrocaseous disease in 1952, which was complicated by incomplete re-expansion. She was discharged with a large apical space and was re-admitted 2 years later with positive sputum, drug resistant organisms, and a persistent right apical space. Bronchography revealed a large right upper lobe stump communicating with the apical space (Fig. 1).

The right chest was re-opened and a large empyema pocket was mobilized extrapleurally. The long residual stump was amputated, flush with the main bronchus, and closed with No. 36 wire on an atraumatic Sellors needle. The apical segment of the lower lobe, which was grossly involved in fibronodular disease, was resected. Both the stumps were carefully covered with viable peribronchial tissues. The procedure was completed with a five-rib osteoplastic thoracoplasty to obliterate the dead space. Recovery was uneventful, sputum became negative, and the patient was subsequently discharged well.

Comment.—In the presence of a long stump and a large apical space, conservative management over a 2-year period was not effective and, indeed,

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should not have been persisted with. Re-amputation of the bronchus stump, combined with a space-reducing procedure, was the only alternative.

CASE 2.—S. C., a 42-year-old man, had been treated since late 1930 for cavitary disease in the right upper lobe and apical segment of lower lobe. Eight-rib thoracoplasty in stages

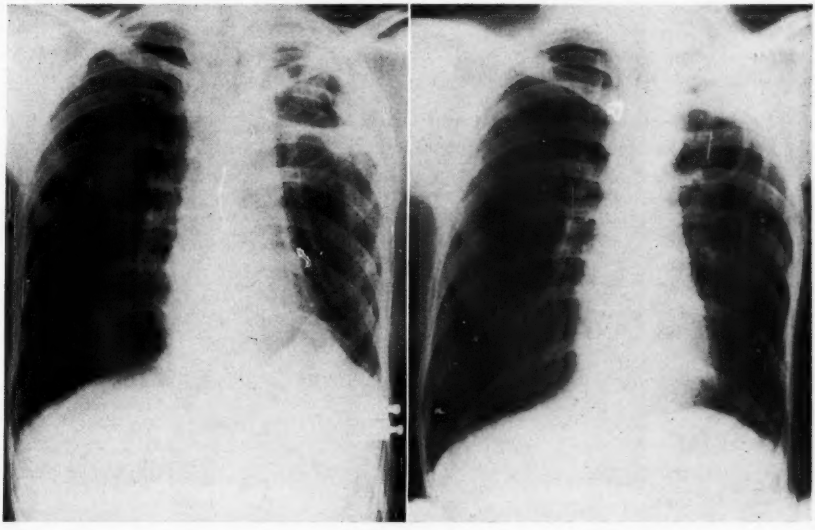
Fig. 1.—(Case 1, F. S.) Bronchogenic demonstration of the long residual stump of the right upper lobe bronchus.

Fig. 2.—(Case 2, S. C.) Sinogram which demonstrates the long residual right main-stem bronchus.

failed to convert sputum. In 1953, he was still sputum positive and now drug resistant. A right pneumonectomy was performed. Resection was complicated by bronchopleural fistula. Conservative management, including tube drainage, broad spectrum antibiotics, and all available antituberculous drugs, failed to heal the fistula. During the next 4 years the sputum remained positive and there were several episodes of contralateral spread.

This patient came under our care in 1957 with a bronchopleurocutaneous fistula, a positive sputum, and resistance to all drugs. Bronchoscopy and sinogram showed a long bronchus stump. At the time of pneumonectomy, the upper and lower lobe bronchi had been closed separately, thus leaving a stump at least 4 cm. in length (Fig. 2).

The right chest was re-opened through a posterolateral incision. Several hours were spent in mobilizing the fistulous tract. No anatomic landmarks could be identified and the hilum was a mass of fibrous tissue. At the end of 3 hours, the procedure was abandoned. This patient continues to have a draining sinus and is intermittently positive.



A. *B.*

Fig. 3.—(Case 3, L. B.) *A*, A view of the chest made 5 weeks after conservative management of the bronchopleural fistula. *B*, Posteroanterior view of the chest after a tailoring thoracoplasty.

Comment.—The indication for surgical intervention in this case is clear cut. Technically, however, it was felt to be too hazardous to continue at that time. With increasing experience, this patient could have been approached more favorably through an anterior thoracotomy or a median sternotomy incision. By this approach, the hilar vessels can be ligated inside the pericardium and the right main bronchus and its fistula can be safely approached through more normal tissue planes.

CASE 3.—L. B., a 23-year-old man, was admitted with an open cavitary lesion in the left apex. After 4 months of drug therapy, the left apicoposterior segment was resected by us. Resection was complicated by a staphylococcal empyema and a bronchopleural fistula. Intercostal tube drainage and massive doses of broad spectrum antibiotics were immediately instituted. Six weeks later, a standard five-rib thoracoplasty was performed. Following this, the fistula healed. The patient was subsequently discharged cured.

Comment.—In this case, 6 weeks of conservative treatment with tube drainage and antibiotics failed to heal the fistula. More active surgical measures were necessary.

CASE 4.—J. W., a 46-year-old man, had been in the sanatorium for over 10 years and at one time had far-advanced disease involving both lungs. The disease in the left lung had been arrested following a seven-rib thoracoplasty. The presenting problem was a destroyed right upper lobe and apical segment of the lower lobe with cavitation. Sputum was positive and drug resistant. Ventilation studies showed a total vital capacity of 45 per cent and maximum breathing capacity of 16 per cent of predicted values. The right upper lobe and apical segment of the lower lobe were resected and a five-rib tailoring thoracoplasty performed by us. During the early postoperative period, the right upper lobe bronchus broke down. Tube drainage and broad spectrum antibiotics were immediately started. Tracheotomy was done to combat ventilatory insufficiency and prevent contralateral spillage. After 6 weeks, there was no improvement, so the stump, which had been originally closed with silk, was re-exposed, sutured with wire, covered with a viable muscle graft and a Schede thoracoplasty was performed. Two weeks later death occurred from sudden uncontrollable hemorrhage inside the right chest.

Comment.—Permission for autopsy in this case could not be obtained. The cause of the hemorrhage is not definitely known, but very likely this was secondary hemorrhage from the pulmonary artery in an infected space.

CASE 5.—E. T., a 38-year-old woman, had been in the sanatorium for over 9 years and had been through five thoracotomies involving both sides. In 1956, she had presented with a positive sputum and drug resistant organisms. A bronchogram showed a bronchopleural fistula from the left apicoposterior stump communicating with an empyema pocket extending up under the thoracoplasty (Fig. 4). The left chest was re-opened and the remainder of the left upper lobe, together with the empyema pocket, was mobilized extrapleurally. The left upper lobe bronchus was divided flush with the main bronchus. The bronchus stump was closed with wire and then covered by a muscle graft. The existing apical thoracoplasty was revised and extended. She made an uneventful recovery and was later discharged.

Comment.—Eighteen months after discharge she returned with *one* positive sputum. Further investigations failed to show either reactivation or recurrence of fistula.

CASE 6.—L. W., an 18-year-old girl, was admitted in 1950 with a tuberculoma in the apical segment of the left lower lobe and was treated by segmental resection. Resection was complicated by massive atelectasis, empyema, and bronchopleural fistula. Four years later, a left pneumonectomy was performed because of persistent fistula. Infection of the left pleural space persisted and the bronchus stump broke down. Seven-rib thoracoplasty in stages was followed with an immediate good result. One year later she developed a draining sinus and sputum became positive again. Bronchoscopy and bronchography showed a long left main-stem bronchus stump communicating with the skin. Through a left anterior thoracotomy, the hilum was explored. The left pulmonary artery was ligated inside the pericardium, then the bronchus stump was isolated and dissected up to the carina. The fistulous stump was amputated flush with the trachea and closed with wire. This girl made an uneventful recovery.

Comment.—A standard posterolateral approach in this case would have presented technical problems similar to those encountered in Case 2.

CASE 7.—J. T., a 28-year-old man, underwent right upper lobectomy for a cavitary lesion. Resection was complicated by empyema and bronchopleural fistula. A tailoring thoracoplasty 4 weeks later failed to heal the fistula. About 18 months later, the fistula was explored and

the bronchus stump was re-amputated and the thoracoplasty revised and extended. The fistula recurred. In spite of tube drainage and antibiotics, the patient continued to go downhill and had repeated contralateral spreads. At this stage, the patient came under our care. We recommended right pneumonectomy, which was not acceptable to the patient who soon afterward left the sanatorium against advice.

CASE 8.—L. C., a 35-year-old man, with severe diabetes, was admitted in September, 1951, with cavitary disease in the left upper lobe and was treated with a left upper lobectomy after 6 months of chemotherapy. Recovery was uneventful. He was re-admitted in 1955 with cavitation in the apical segment of the left lower lobe. Following a course of antituberculous drugs, a left pneumonectomy was performed in November, 1956. This was complicated by bronchopleurocutaneous fistula. Eight-rib thoracoplasty in stages and a stage of Schede thoracoplasty failed to heal the fistula. Two episodes of contralateral spread

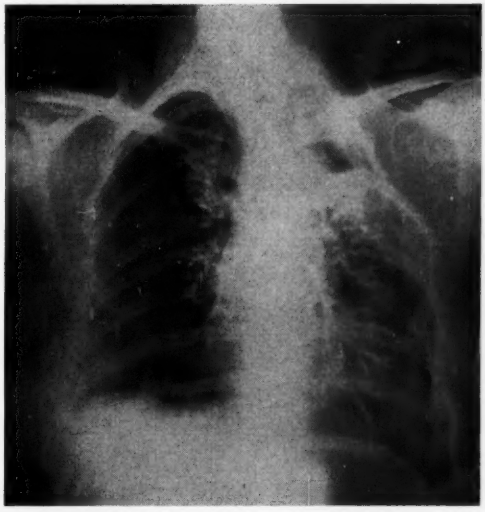
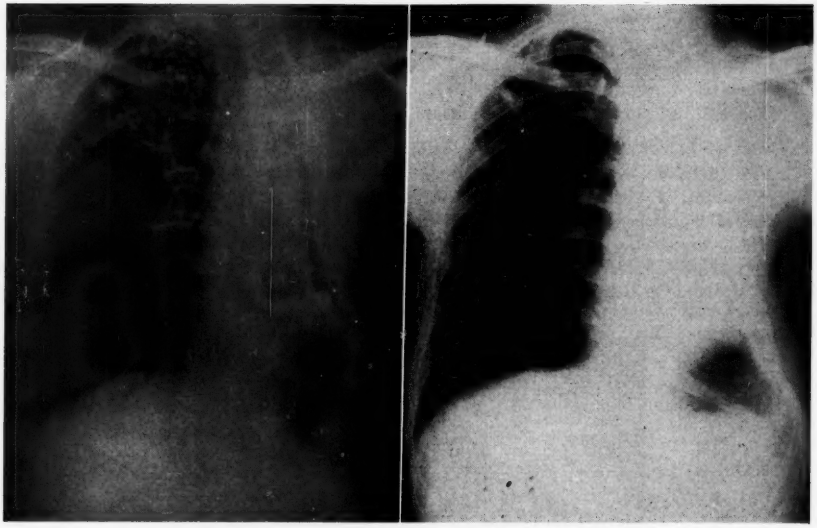


Fig. 4.—(Case 5, E. T.) Bronchographic demonstration of the fistula extending up under the thoracoplasty.

occurred. In late 1958, this patient was presented to us with positive sputum, positive draining sinus, and drug resistant organisms. A long left bronchus stump, communicating through an empyema pocket to the skin on the chest wall, was demonstrated (Fig. 5).

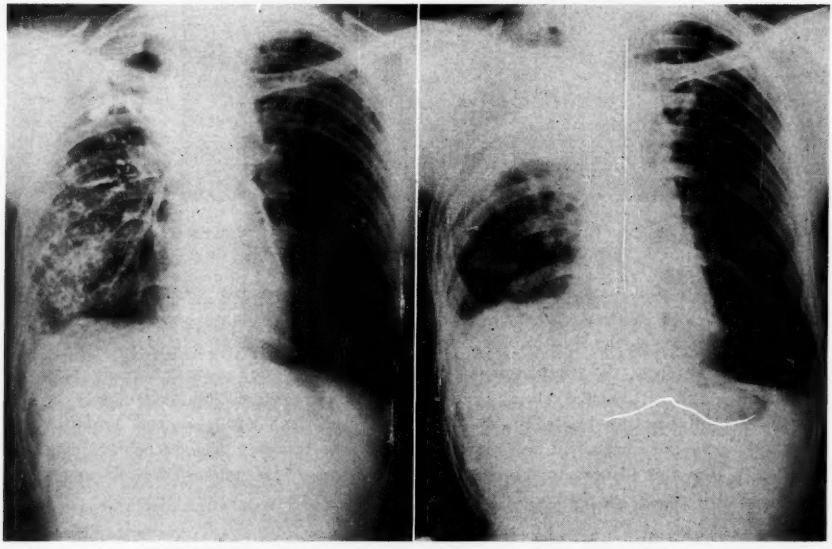
Re-amputation of the fistulous stump was carried out through a left anterior L-shaped incision dividing 3, 4, and 5 costal cartilages. The pericardium was deliberately opened and the left hilar vessels ligated inside the pericardium. The left main-stem bronchus was mobilized up to the carina and transected flush with the trachea. The bronchus stump was closed with wire and adequately covered with viable tissue. This patient made an uneventful recovery and is ready for discharge.

Comment.—In this case it was clearly demonstrated that it would have been difficult if not impossible to revise the bronchus stump through a classical posterolateral approach. Again it would have been extremely dangerous to dissect the bronchus without prior ligation of the pulmonary artery and veins, since all these structures were densely bound by fibrous scar tissue to the region of the bronchus stump.



A. *B.*

Fig. 5.—(Case 8, L. C.) *A*, Roentgenogram of the chest, following a sinogram, which demonstrates a long left bronchus stump and a normal right bronchial tree. *B*, Postoperative x-ray study after the fistula has closed.



A. *B.*

Fig. 6.—(Case 9, S. G.) *A*, Bronchographic demonstration of the fistula in the right upper lobe bronchus stump communicating with the apical space. *B*, Postoperative roentgenogram.

CASE 9.—S. G., a 29-year- old man, was treated for bilateral apical disease from 1950 to 1954, and re-admitted in 1956 with reactivation of disease. After 14 months of treatment with drugs, a right upper lobectomy was carried out. A residual space persisted and the sputum became positive. Bronchography revealed a bronchopleural fistula (Fig. 6).

The right chest was re-opened and the empyema sac was mobilized extrapleurally. The bronchus stump was re-amputated, flush with the main bronchus, and closed with wire. After covering the stump, a five-rib osteoplastic thoracoplasty was performed. There was an uncomplicated recovery.

Comment.—The right upper lobe bronchus stump breaks down more frequently as is noted in Cases 1, 4, and 7, but, as the right upper lobe is the commonest lobe to be resected for pulmonary tuberculosis, this susceptibility may be more apparent than real.

CASE 10.—R. M., a 54-year-old man, was treated with drugs for 2 years for a right apicoposterior lesion. The lesion was removed by a large wedge resection. Following resection, sputum became positive and a small apical pocket persisted. Bronchography revealed a bronchopleural fistula communicating with the apical pocket.

The right chest was re-opened and the remainder of the upper lobe along with the apical empyema was mobilized extrapleurally. The upper lobe bronchus was divided flush with the main bronchus and closed with wire. After covering the stump with a large pedicled pleural flap, a tailoring thoracoplasty was done. The postoperative course was complicated by severe paradoxical breathing, recurrent atelectasis, and ventilatory insufficiency but these responded to tracheostomy and chest strapping.

Comment.—In this elderly man, a standard tailoring thoracoplasty was performed instead of the osteoplastic type, which we prefer, because the latter procedure is more time consuming and the patient's condition on the table was deteriorating. A tracheostomy 2 days later was a life-saving procedure.

DISCUSSION

The management of bronchopleural fistula is still a controversial subject. Pacheco and his associates[4] recommend conservative management while others[5] favor immediate re-operation. Conservative management is probably worth a trial initially. When a fistula is recognized, simple intercostal tube drainage should be immediately instituted to minimize spillage into the remainder of the lung or the contralateral lung. The problem of spillage assumes grave significance when fistula occurs in a pneumonectomy stump. As a prophylaxis, in all pneumonectomies, it has been our practice to keep the pleural space dry for 2 to 3 weeks. When a partial resection is complicated by fistula, intercostal tube drainage and negative suction is instituted immediately in an attempt to re-expand the remainder of the lung and obliterate the pleural space. Broad spectrum antibiotics are used liberally to combat the almost inevitable superimposed pyogenic infection.

Tube drainage and antibiotics constitute the early conservative therapy. A small leak occurring in a segmental stump is very likely to heal with this regimen. A fistula in a major bronchus may close only temporarily, leaving a residual pleural space. It is probably acceptable to continue conservative management of such a space in the nontuberculous patient. In a tuberculous

patient, however, the fistula may remain masked temporarily but, in time, the majority of these patients will return with a positive sputum, drug resistant organisms, and possibly spread to other areas. Once a major fistula becomes established, definitive surgical methods should be resorted to after 4 to 6 weeks. Each patient with a bronchopleural fistula presents a different problem and, as such, no generalization in their surgical management can be made.

Established bronchopleural fistulas can be broadly separated into three groups:

(1) *Fistula occurring after segmental resection:* This is usually seen after apical or apicoposterior segmental resection. If recognized early and treated with tube drainage and suction, the majority of these will close if superimposed infection can be controlled. If the fistula does not heal in 4 to 6 weeks, a standard or osteoplastic thoracoplasty will close the fistula. Rarely, if the fistula has been long standing and associated with a thick empyema sac, will thoracoplasty alone be inadequate but must be combined with decortication of the sac.

(2) *Fistula occurring in a major bronchus following lobectomy:* For some reason the right upper lobe stump seems to be more vulnerable to breakdown. In spite of initial treatment with drainage, suction, and antibiotics, the fistula is more likely to persist and more active surgical measures will be necessary. Complete excision of the infected space, re-amputation of the fistulous stump, if long, and a space-reducing procedure are all necessary for a satisfactory result.

(3) *Fistula in a pneumonectomy stump:* Three of the above cases were in pneumonectomy stumps. These patients had a very long term, indeed too long a trial, of conservative treatment. Drug resistant organisms, positive sputum, a draining sinus, low-grade sepsis, and repeated contralateral spread are the dominant features in them. Re-amputation of the bronchus stump, closure with wire, adequate coverage of the bronchus, and obliteration of the pleural space will close the fistula in most instances.

In all 3 patients with fistulas following pneumonectomy, multiple stages of thoracoplasty had been performed several years before. These cases present considerable technical difficulty. Long-standing sepsis makes it virtually impossible to isolate the vascular structures in the distorted hilum, and, because of this, the bronchus stump cannot be dissected with safety. Under such circumstances it is our practice now to approach the hilum through a median sterniotomy or an anterior thoracotomy and to re-ligate the pulmonary artery and veins inside the pericardium as the first step. After this, the bronchus stump can be dissected up to the carina with impunity and the repair completed with relatively little risk. It is felt that an anterior approach such as this, with control of the major vessels from within the pericardial sac, will allow more of these complicated fistulas to be successfully eliminated.

In the final analysis, the management of bronchopleural fistulas is preventive. More careful attention to the bronchus stump initially will reduce

the number of breakdowns to an irreducible minimum. Thus, it behooves one to reiterate the principles of bronchus closure. These are—as short a bronchus stump as possible, a viable stump, as little suture material as possible, preferably of wire, and careful coverage of the bronchus with a viable pleural, pericardial or muscle flap.[1] These measures, combined with the principles of surgical technique as usually practiced, will improve the still too high incidence of bronchopleural fistula.

SUMMARY

The management of 10 cases of bronchopleural fistula is discussed. Eight of these were long-standing cases.

Four occurred following right upper lobectomy, 3 following pneumonectomy, 2 following resection of the left apicoposterior segments, and 1 after a large wedge resection of the right apex.

One patient (Case 4) died, 1 (Case 7) refused further surgery, in 1 (Case 2) the fistula could not be closed. The remaining 7 healed following active surgical measures.

If the fistula persists after 4 to 6 weeks of conservative treatment with tube drainage and antibiotics, more definitive surgical procedures should be adopted forthwith. The principles of bronchus closure are re-stated as the real management of bronchopleural fistula is preventive.

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MEDIASTINAL TERATOMA IN INFANCY

Report of Successful Removal From Premature Infant and Review of Literature

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THE DEVELOPMENTS in thoracic surgery during the past two decades and the more frequent use of periodic chest x-ray examinations have stimulated renewed interest in teratomas of the mediastinum. The literature on the subject largely concerns adults, with a relatively small number of cases reported in childhood. In infancy, the tumor is a comparative rarity, and only a few tumors have been successfully removed during this early period of life. Today, it should be possible to remove safely most large symptomatic mediastinal teratomas in infants if the condition is suspected and surgery is undertaken without unnecessary procrastination.

After the gonads, the mediastinum is the most common site for teratomas in man. These tumors have been the center of great interest in the past because of their extraordinary morphology. Their true incidence in relation to other primary tumors of the mediastinum varies among different reported series. In general, however, they rank second after neurogenic tumors, although, in some reviews, tumors of the thymus occupy this position. Granulomas and lymphomas are not considered in this review of primary mediastinal tumors.

The comparative incidence of primary mediastinal tumors differs in some areas between the infant and the adult. Teratoma appears to be the most common tumor occurring in the anterior mediastinum of infants and children. Although the thymus casts a prominent mediastinal shadow during the first year or two of life, true thymomas are uncommon in infants. Two other relatively common anterior mediastinal tumors found in adults—substernal thyroids and pericardial cysts—are rarely encountered in infants.

Recent experience with a large mediastinal teratoma which was successfully removed from a 2-day-old premature infant stimulated our interest in this subject. From a review of all available literature, this appears to be the youngest individual from whom such a tumor has been successfully removed. After a short period of temporary improvement, the infant developed progressively severe respiratory distress due to a paralyzed left diaphragm. This

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desperate situation was corrected surgically by infolding the diaphragm, using a reinforcing prosthesis of knitted Dacron mesh. Because of the rarity of this tumor in the newborn and certain interesting features encountered in this patient, it was felt worth while to record this experience and to review the pertinent literature.

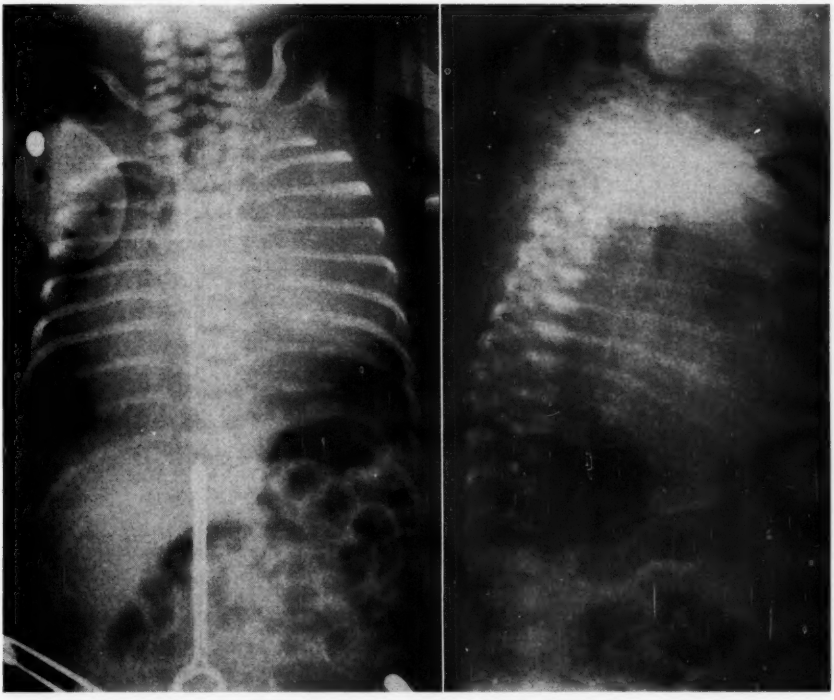

Fig. 1.—Chest roentgenograms made Nov. 24, 1958. Posteroanterior and lateral views which show large mediastinal teratoma.

CASE REPORT

J. F., a white female was born prematurely in the Buffalo Children's Hospital on Nov. 22, 1958, in the seventh month of pregnancy, following spontaneous rupture of the membranes. The pregnancy otherwise had been uneventful. Birth weight was 5 pounds, 7 ounces. The obstetrician commented upon the excess mucous and costal retraction. In the premature nursery, the infant's color was dusky when temporarily removed from the Isolette. During the first day, moderate respiratory distress continued with xyphoid retraction and transient episodes of cyanosis. Breath sounds were noted to be diminished over the left chest. No cardiac bruits were heard. The possibilities of atelectasis or hyaline membrane disease were entertained. On the second day, the left hemithorax was noted to be dull to percussion with absent breath sounds. Chest x-ray studies obtained that afternoon, Nov. 24, 1958, showed a large homogeneous mass with a sharp lower border. The mass occupied most of the left hemithorax displacing the mediastinum to the right (Fig. 1). The infant was taken to the operating room that evening with a preoperative

diagnosis of mediastinal cyst or tumor. A nasogastric tube passed easily into stomach, but no special diagnostic studies were performed because of the precarious condition of the infant.

The chest was opened through the complete length of the fifth interspace. A well-encapsulated dark, red, solid mass, which practically filled the entire left hemithorax, presented. It was necessary to divide the fifth rib to expose adequately the base of this mass. A number of large vessels entering the tumor from the mediastinum were divided. A one centimeter adherent piece of pericardium was removed with the tumor. A relatively normal-sized thymus remained undisturbed in the anterior mediastinum. The

Fig. 2.

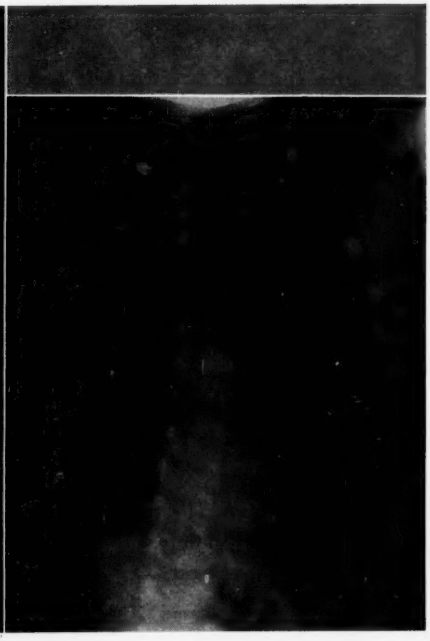

Fig. 3.

Fig. 2.—Chest roentgenogram made Nov. 24, 1958, immediately following removal of mediastinal teratoma.

Fig. 3.—Chest roentgenogram made on Dec. 15, 1958. Heart remains shifted to the right. Left hemidiaphragm becoming progressively elevated.

entire left lung, which had been compressed inferiorly, now expanded well with massage and gentle positive pressure. For no apparent reason, the heart remained largely in the right hemithorax after the tumor was removed. The vessels that had coursed to the tumor appeared to originate from the mid-anterior and superior areas of the mediastinum. Because of the infant's unstable condition the mediastinum was not examined further. The immediate postoperative chest roentgenogram showed the left lung to be well expanded and the left diaphragm not elevated. The heart remained largely shifted to the right (Fig. 2).

During the first few postoperative days the infant breathed feebly, but the respiratory status improved thereafter. During the second postoperative week, however, the nurses noted occasional episodes of duskiness. Chest x-ray studies showed progressive elevation of the left hemidiaphragm (Fig. 3). By Dec. 24, 1958, the weight had dropped to 4 pounds, 9 ounces. The number of cyanotic spells had increased and the infant was

showing considerable respiratory distress. The left hemithorax moved less than the right. The cardiac silhouette remained largely to the right. There was disagreement as to whether this represented persistent mediastinal shift or dextrocardia. The left diaphragm remained elevated and was motionless under fluoroscopy. An almost fatal episode of severe cyanosis and apnea resolved the period of indecision as to whether the infant should be subjected to surgery for correction of the elevated left diaphragm.

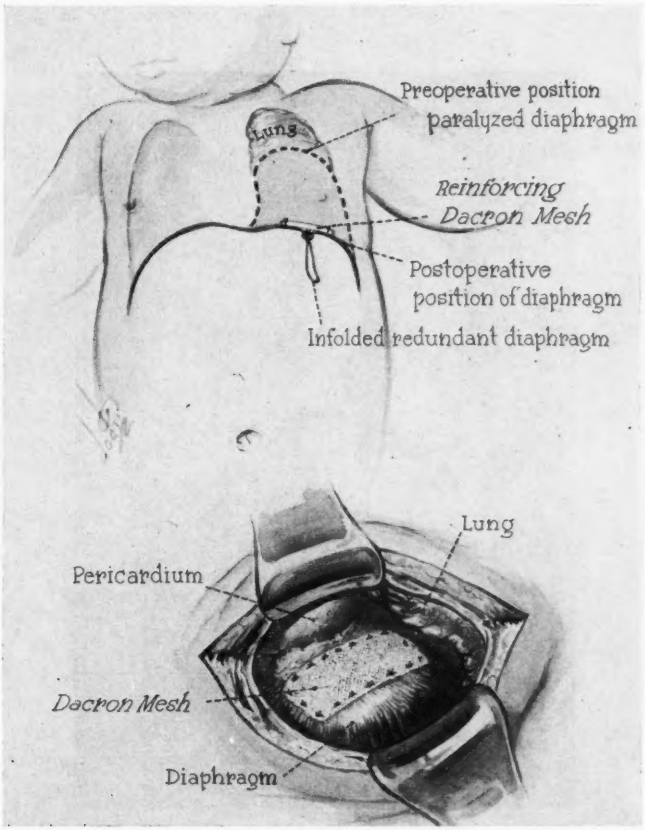

Fig. 4.—Diagrammatic representation to show method of repair of paralyzed diaphragm (see text).

On Dec. 27, 1958, thoracotomy was performed through the left seventh interspace. The elevated diaphragm filled the lower two thirds of the hemithorax. Adhesions between lung and diaphragm were divided and the dome of the diaphragm could then be depressed. The diaphragm was flaccid but it did not appear thin as with true eventration. The distal 2 cm. of the phrenic nerve, visible through this exposure, appeared normal. There was no response when stimulated by an electric current. The diaphragm muscle contracted weakly when electric current was applied directly to it. The redundant flaccid diaphragm was depressed inferiorly and the edges of the infolded area sutured together with interrupted silk leaving the diaphragm flat and tautly stretched between the costal attachments. The single suture line was reinforced by a patch of knitted Dacron mesh

(Fig. 4). This allowed the operation to be accomplished quickly and without need for exposing the abdominal contents through an opening in the diaphragm. The left lung was then freed from its costal adhesions, allowing it to expand inferiorly and fill the hemithorax down to the new low position of the diaphragm.

Postoperatively there was a dramatic change to a quiet regular type of respiration. The infant did well and gained weight. The last x-ray study before discharge showed the left hemidiaphragm in satisfactory position and the mediastinum returning to the left (Fig. 5). When last seen in April, 1959, she was an active healthy baby weighing 10 pounds.

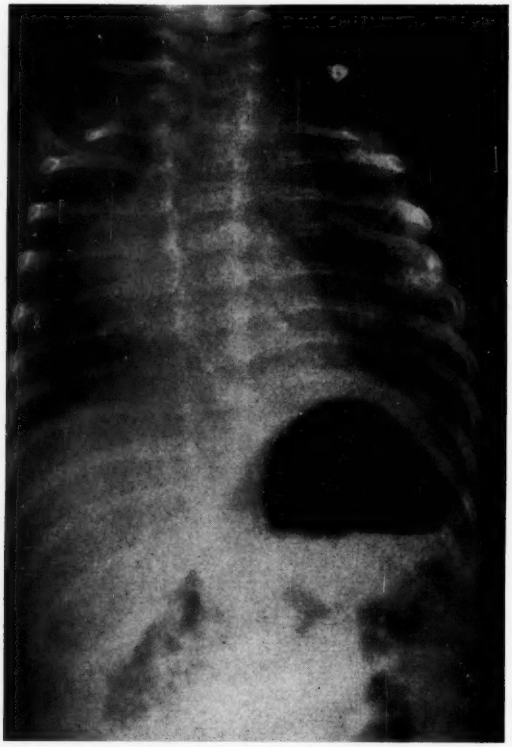

Fig. 5.—Chest roentgenogram made on Jan. 10, 1959, two weeks following repair of paralyzed left diaphragm.

*Pathologic Report.**—The teratoma was grossly a nodular, rounded tumor with a serous capsule, measuring 5.8 by 4.5 by 4.1 cm. as received in the frozen state. On the cut surface, the tumor had multiple cystic spaces containing mucoid- and colloid-like material (Fig. 6). Except for the more grayish-white color, the tumor resembled somewhat a colloid cystic goiter; neither bony nor epidermoid structures were seen.

Microscopically, this was a typical adult teratoma, consisting for the most part of derivatives of the entoderm with numerous glands and cysts lined by mucus-secreting epithelium. Groups of liver cells of varying size, and individual glands resembling bile ducts and pancreatic glands, were seen between the cysts. The intervening stroma contained markedly

*Abstracted from the report by Dr. Kornel Terplan, Professor and Chairman of the Department of Pathology, University of Buffalo School of Medicine.

edematous mesenchymal structures, including numerous smooth muscle fibers, some fat tissue, and capillary vessels. Of particular interest, and somewhat outside of the general structural frame of this teratoma, was the finding of melanin pigment in the epithelial lining of two cysts, resembling the epithelium of the retina. The presence of this pigment points to some ectodermal analage. No undifferentiated or embryonal structures were seen. There was no anaplasia of any sort. Some cysts were lined by striated columnar epithelium resembling the mucosa of the respiratory tract.

DISCUSSION

I. *Mediastinal Teratoma.*—Today most authorities prefer to erase the earlier idea of a distinction between mediastinal dermoid cysts and teratomas because of the frequency with which teratomatous elements can be demonstrated when

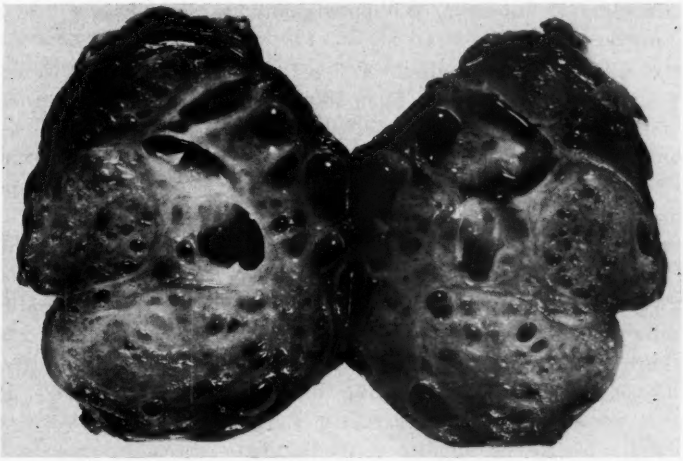

Fig. 6.—Gross appearance of mediastinal teratoma (cut section).

dermoid cysts are subjected to comprehensive examination. These lesions may be collectively called teratoid tumors or else referred to as cystic and solid teratomas. Cystic teratomas outnumber the solid ones. The solid tumors are more complex, however, and have a greater propensity for malignant change. The incidence of malignancy for both types has been quoted as from 10 to 33 per cent, but a figure around 20 per cent would appear to be an acceptable average.

The etiology of teratomas has been a subject for considerable speculation, but no single opinion is as yet universally accepted. Perhaps the most plausible theory of the genesis of extragonadal teratomas is that they are the result of local dislocation of tissue during embryogenesis. In discussing mediastinal teratomas, Schlumberger[24] incriminates the branchial clefts, specifically tissue dislocations in the anlage of the thymus. It has been stated that the thymus is the only branchiogenic structure to descend routinely into the mediastinum and also one that may give rise to derivatives of all three germinal

layers. The close association with the thymus would also explain in part why most teratomas occur in the anterior mediastinum.

It is generally stated that there is no appreciable difference in the sex incidences of these tumors. Ochsner,[18] however, has said that in children there is a great preponderance of females. Although many tumors are asymptomatic at the time of discovery, the majority will eventually give rise to symptoms and contribute to the death of the individual.[22] The tumors usually cause symptoms because of pressure on or erosion into nearby structures. Less commonly, the individual may cough up hair or other suspicious material. Occasionally, a cystic lesion may become infected and perforate into the lung or pleura. In general, the tumors grow slowly and remain asymptomatic for years. It has been suggested that some teratomas receive a growth stimulus around the time of puberty. With malignant change, however, the growth process may be greatly accelerated.

The tumors are usually discovered between the ages of 20 to 40 years, either because of symptoms or, commonly, as a result of routine roentgenograms of the chest in an asymptomatic individual. Most published series on mediastinal teratomas concern adults with little or no mention of its occurrence in infants and young children. With few exceptions,[7, 10] the reports on mediastinal teratomas in infants have consisted mostly of single case reports. In several papers published about the turn of this century, it is difficult to determine whether the lesions were teratoid tumors or bronchogenic, enterogenous, or other types of cystic and solid malformations. A few reports dealing with the broader subject of mediastinal tumors and teratomas refer to infants or young children only by stating the oldest and youngest subject in the series or else by general age grouping, listing the number under 20 years or 12 years of age. It becomes apparent, therefore, that it is not possible to state an absolute figure as to the number of mediastinal teratomas found in infancy in the literature. Nevertheless, it is of interest to review briefly the available literature on mediastinal teratomas in infancy.

Approximately 26 extrapericardial teratomas occurring in infancy have been found in our review of the literature. In this connection, infancy has been taken as a period under 2 years of age. Because of incomplete documentation in two collective reviews, it is possible that several references to a few early cases may overlap (Table I).

TABLE I. MEDIASTINAL TERATOMAS OF INFANCY

AUTHORS AND DATES	NO. PATIENTS	AGES	COMMENTS
Kerr and Warfield,[16] 1928	3	First year of life	Literature review
Poynton,[20] 1929	1	4 mo.	Autopsy; no operation
Wilcox and Wollstein,[29] 1931	1	6 mo.	Autopsy; no operation
Struthers,[26] 1932	1	5 mo.	Autopsy; no operation
Hedblom,[11] 1933	6	3-8 mo.	Collective review
Rusby,[22] 1944	1	16 mo.	Autopsy; malignant teratoma
Laipply,[17] 1945	1	"Stillborn"	No details
Total	14		

With one exception,[28] the 12 infants with mediastinal teratomas surgically removed have been reported during the past decade (Table II).

TABLE II. MEDIASTINAL TERATOMAS OF INFANCY

AUTHORS AND DATES	NO. PATIENTS	AGES	COMMENTS
Wheatley,[28] 1937	1	7 mo.	Died following surgery
Vervat,[27] 1949	1	8 mo.	Successfully removed
Gross,[10] 1953	3	2, 19, 21 mo.	Successfully removed
Starer,[25] 1954	1	10 da.	Successfully removed
Sarinana et al.,[23] 1954	1	2 mo.	Successfully removed
Peabody et al.,[19] 1954	1	4 mo.	Successfully removed
Ellis et al.,[7] 1955	3	3 wk.; 3, 5 mo.	Successfully removed
Herlitzka and Gale,[12] 1958	1	3 mo.	No details
Total	12		

A word should be included about the so-called intrapericardial teratomas. Actually these tumors are also mediastinal and some have considered them to be similar to the more common anterior mediastinal extrapericardial teratomas with a chance location inside rather than outside the pericardium. It is of interest that most of these tumors have been found in infancy or childhood, in contrast to the extrapericardial mediastinal teratomas which are usually found in adults. It may be that the intrapericardial tumors become apparent at an earlier age because they are contained in closer proximity to the heart and great vessels and even a small tumor mass may give rise to noticeable signs and symptoms. A review of the literature revealed nine intrapericardial teratomas, six occurring in infancy (Table III).

TABLE III. INTRAPERICARDIAL MEDIASTINAL TERATOMAS

AUTHORS AND DATES	NO. PATIENTS	AGES	COMMENTS
Grimm,[9] 1927	1	3 mo.	Died; no surgery
Jellen and Fisher,[14] 1936	1	3 wk.	Died; no surgery
Willis,[30] 1946	1	10 wk.	Died; no surgery
Claireaux,[6] 1951	1	Premature newborn	Died; no surgery
Basora-Defillo and Lichtenberg,[3] 1956	1	15 da.	Died; no surgery
Richards and Reeves,[21] 1958	1	3 mo.	Successfully removed
	Children and Adults		
Joel,[15] 1890	1	14 yr.	No details
Beck,[4] 1942	1	22 yr.	Successfully removed
Gebauer,[8] 1943	1	12 year	Died; hemorrhage at surgery
Total	9		

The intimate association of intrapericardial teratomas with the heart or great vessel becomes of great practical importance when such tumors are to be surgically removed. This was dramatically shown in the report of Gebauer[8] in which fatal hemorrhage occurred when the first portion of the aorta was inadvertently perforated while attempting to remove an intrapericardial teratoma, adherent to this site, in a 12-year-old girl. In a number of autopsy dissections, the intrapericardial teratoma has been described as attached to the adventitia of the great vessels by a stalk which would have presented a less hazardous technical problem at surgery.

It seems reasonable to assume that most if not all mediastinal teratomas are present at birth. The true incidence of this tumor in infancy might be more accurately appraised if all infants were subjected to routine chest x-ray studies. Unless special projections were taken, however, small tumors might be missed at this early age with a routine posteroanterior chest film as taken in adult surveys. Certainly one would not recommend unnecessary x-ray exposure to normal asymptomatic infants merely in an effort to detect a mediastinal teratoma.

Practically all mediastinal teratomas in infancy have been found because they caused signs and symptoms or else they were discovered at postmortem examination. Cough, dyspnea, and cyanotic episodes are the predominant symptoms in infants. Other findings are occasionally encountered as a result of pressure, perforation, or infection. With large tumors filling the hemithorax, the involved side may lag with respiration and show protruding intercostal spaces. The percussion note will be flat with diminished breath sounds and the displaced maximum cardiac impulse may reflect a mediastinal shift. A roentgenogram of the chest will usually show a dense rounded mass with sharply defined borders projecting laterally into either hemithorax and blending centrally with a mediastinal cardiac shadow, usually located in the anterior mediastinum. If the mass contains plaques of calcium or a tooth, the diagnosis becomes quite certain.

Unless the tumor is intimately adherent to the heart or aorta, as with intrapericardial teratomas, the mass is frequently well circumscribed and easily shelled out from its surroundings at operation. With infection, perforation, or malignant degeneration, complete removal may be difficult or impossible. Certain diagnostic and therapeutic procedures used before the development of modern thoracic surgery, such as needle aspirations, drainage and decompression, and marsupialization will rarely be indicated. Once the lesion has been demonstrated it should be excised to relieve symptoms and to avoid further complications and malignant degeneration.

Various derivatives of all three germ layers may be found in these tumors. Of interest is the finding of pancreas and thymus in a considerable number of the more solid tumors.[13] The case presented in this paper had pancreas in the teratoma but it was free of any thymic tissue. There was no connection with the thymus gland.

II. *Paralyzed Left Hemidiaphragm.*—There were no signs of brachial plexus injury or other evidence to suggest that a birth injury could have been the cause of the paralyzed diaphragm, a so-called acquired eventration. Although the diaphragm appeared to be near normal position immediately following removal of the tumor, it became progressively elevated during the following 4 weeks causing increasing respiratory disturbance. In this case, the most probable cause of the paralyzed diaphragm would appear to have been inadvertent trauma to the phrenic nerve during removal of the teratoma. In retrospect, the paralyzed diaphragm should have been repaired by surgery earlier.

Disappearance of the severe dyspnea following operative return of the left hemidiaphragm to a lowered position was quite dramatic. The left lung could not fully expand to fill the space that had been occupied by the elevated hemidiaphragm until adhesions between lung and chest wall as a result of previous thoracotomy, were separated. The lung then expanded easily to fill the entire left hemithorax. The infant breathed normally thereafter, although the diaphragm remained motionless.

In discussing eventration of the diaphragm in infancy, Bishop and Koop[5] recently emphasized the relief of respiratory distress that follows the lowering of a paralyzed diaphragm. These authors recommend excising a generous full-thickness ellipse from the central area of the diaphragm and imbricating the free edges. Others have used plication, especially in true eventration presenting a thin or atropic diaphragm, without incising the diaphragm. We decided against opening the diaphragm because of the extra time required for hemostasis and suturing in this critically dyspneic infant. It also eliminated the necessity of depressing abdominal viscera that might tend to herniate upward, as well as reduce the possibility of accidental injury to the spleen.

A low thoracotomy approach allowed proper inversion of the elevated diaphragm resulting in a central fold where the redundant dome was depressed into the abdomen. A row of interrupted sutures, quickly placed, held the diaphragm in this flattened, depressed position. The suture line was then reinforced by suturing a patch of knitted Dacron mesh to the diaphragm around this area. Our experience with this form of pliable synthetic mesh for reinforcing tissue deficiencies of the diaphragm has been most satisfactory to date.[1, 2] Admittedly, this also could have been repaired by imbricating the redundant muscular diaphragm dome which might have added a little extra intrathoracic bulk at the diaphragm level. The point to be stressed, however, is the need for recognizing that severe respiratory distress may be associated with a paralyzed diaphragm in infancy and that the condition may be effectively corrected by a relatively simple operative procedure of lowering the elevated diaphragm.

SUMMARY

1. A large mediastinal teratoma was successfully removed from a premature infant 2 days after birth.

2. A paralyzed left diaphragm (acquired eventration) was repaired several weeks after the teratoma had been removed by using a reinforcing patch of knitted Dacron mesh. Dyspnea dramatically disappeared following repair of the elevated diaphragm.

3. The literature on mediastinal teratoma in infancy, both inside and outside the pericardium, is reviewed. Points of interest from this case and the literature are discussed.

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RESECTIONAL THERAPY FOR PULMONARY TUBERCULOSIS AT SUNMOUNT, 1950-1957, 807 CASES

III. An Evaluation of the Technique of Reconstitution of the Lung in Segmental Resections

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THE PROBLEM of what to do with the raw surfaces of the lung after a segmental resection is still a matter of some controversy. In 1956, Dr. Bell[1] reviewed the different thoughts on this subject and, at the same time, described his technique of reconstitution of the lung.

By reconstitution is meant the approximation of raw surfaces, the obliteration of intrapulmonary dead space, and the burying of the bronchial stump in lung tissue. As a result, no raw surfaces, but only pleural surfaces are allowed to come in contact with the parietal pleura. It was Dr. Bell's clinical impression that the incidence of postoperative complications, especially space problems, was significantly reduced when the method of reconstitution was used.

To evaluate this clinical impression critically, segmental resections and segmental resections with concomitant wedge resections done at Sunmount between the years 1950 to 1957, inclusive, were studied. During this 8-year period, a total of 348 segmental resections and segmental resections with concomitant wedge resection were performed for pulmonary tuberculosis. In 125 cases, the method of reconstitution, as described by Dr. Bell, was applied. In the other 223 cases, the raw surfaces of the lung were not covered, but were allowed, on expansion, to come in contact with the parietal pleura, and to "seal themselves." The incidence of major and minor complications for these two groups of cases was determined. Table I lists the incidence of space problems and major complications in the presence and absence of reconstitution. Major complications include empyema, fistula, and occult fistula. The difference in the major complication rate in the two groups, 12.1 per cent versus 2.4 per cent, is noteworthy. There were no deaths in the group of patients who had segmental resections with reconstitution, and three deaths in the other group. One of these deaths occurred 3½ months postoperatively when an occult fistula eroded into a pulmonary artery. A second death occurred postoperatively from a bleeding diathesis. The third death occurred 4 days postoperatively from cardiac

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arrest, which was probably precipitated by massive subcutaneous emphysema and air leak which persisted despite complete expansion of the lung according to x-ray evidence. The latter 2 cases are not included under the major complications as defined above. Their addition would raise the total number of serious complications to 29, or 13 per cent.

TABLE I. COMPLICATIONS IN SEGMENTAL RESECTIONS AND SEGMENTAL AND WEDGE RESECTIONS, WITH AND WITHOUT RECONSTITUTION

	POSTOP. SPACE PROBLEMS	MAJOR COMPLICATIONS	OPERATIVE DEATHS
Segmental resections with reconstitution	38	3	0
125 Cases	(30%)	(2.4%)	
Segmental resections without reconstitution	107	27	3
223 Cases	(48%)	(12%)	(1.3%)

The difference in the incidence of space problems in the two groups, 48 per cent versus 30 per cent, does not appear too striking on superficial examination. But if we divide the postoperative space problems into three categories in an attempt to grade the morbidity, the differences become more pronounced. In Table II postoperative space problems have been divided into three categories: (1) spaces which require no further therapy and disappear spontaneously, (2) spaces which require relatively minor additional treatment, namely, intubation, and (3) spaces which require thoracoplasties. The incidence of spaces requiring no additional treatment is the same in the two groups; but space problems which required additional treatment occurred three and a half times more often when reconstitution was not carried out.

TABLE II. SPACE PROBLEMS IN SEGMENTAL RESECTIONS AND SEGMENTAL AND WEDGE RESECTIONS, WITH AND WITHOUT RECONSTITUTION

	SPACE REQUIRING NO SPECIFIC RX	SPACE REQUIRING INTUBATION	SPACE REQUIRING THORACOPLASTY
Segmental resections with reconstitution	30	8	0
125 Cases	(24%)	(6.4%)	
Segmental resections without reconstitution	55	47	5
223 Cases	(25%)	(21%)	(2%)

Since it was a frequent practice at this hospital during the early days of wedge resections to allow raw lung surface to remain after simple wedge resections, it was thought desirable also to study a group of pure segmental resections. By eliminating those cases in which a wedge resection accompanied a segmental resection, the group for evaluation was reduced to 193 cases. In this group, 85 cases represent segmental resections with reconstitution, and 108 cases segmental resections without reconstitution. In Table III the incidence of space problems, space problems requiring treatment, and major complications for the group of pure segmental resections is summarized. The findings here are entirely comparable with those in the larger group which includes concomitant wedge resections.

TABLE III. COMPLICATIONS AND SPACE PROBLEMS IN PURE SEGMENTAL RESECTIONS, WITH AND WITHOUT RECONSTITUTION

	SPACE REQUIRING NO SPECIFIC THERAPY	SPACE REQUIRING INTUBATION	SPACE REQUIRING THORACOPLASTY	MAJOR COMPLICATIONS
Segmental resections with reconstitution 85 Cases	16 (19%)	5 (6%)	0	2 (2.4%)
Segmental resections without reconstitution 108 Cases	29 (27%)	21 (19%)	1 (0.9%)	16 (15%)

DISCUSSION

The above figures clearly indicate that the incidence of space problems, especially serious space problems, and major complications is significantly less when reconstitution is carried out. The fact that the incidence of space problems which require no additional treatment in the two groups of cases is approximately the same suggests that the mechanics of filling space, namely, expansion and shift, are not significantly altered by the technical maneuver of reconstitution. However, the greater incidence of space problems requiring additional treatment in the group without reconstitution suggests that significant troublesome postoperative air leaks are minimized by the technique of reconstitution.

One may now question whether the two groups are comparable in other respects. The anatomic location and number of segments removed in the two groups have been analyzed and found to be completely comparable. It was also found that the extent of the resection did not correlate with either major complications or space problems. As the majority of resections without reconstitution was carried out prior to 1954, there may exist some difference in the chemotherapy coverage available. With this point in mind, chemotherapy coverage in the complications was evaluated. Chemotherapy coverage was graded as good and poor, as defined elsewhere.[2] It was found that 50 per cent of the patients with major complications in the non-reconstitution group had good chemotherapy coverage. Empyemas in this group were nontuberculous by culture. Surprisingly, a large number of patients who had complications while on poor chemotherapy coverage also had nontuberculous empyemas by culture and no subsequent evidence of active tuberculosis. Of the three complications in the group of segmental resections with reconstitution, 2 patients had poor drug coverage, and one patient had good chemotherapy.

The high incidence (50 per cent) of patients with good chemotherapy coverage and complications in the group without reconstitution, and the fact that ten of thirteen empyemas in that group failed to culture tuberculous organisms, strongly suggests that the complications encountered are frequently not due to underlying tuberculosis. These data strongly suggest that the combination of contamination from air leak plus a convenient culture medium supplied by raw lung surface are the offenders.

The complications in the group with reconstitution consisted of two nontuberculous empyemas and an occult fistula in a patient with poor chemotherapy

coverage. Seven occult fistulas are included among the twenty-seven major complications for the combined segmental and wedge resections without reconstitution, while the sixteen major complications in the pure segmental resections without reconstitution include five occult fistulas.

SUMMARY

1. One hundred and twenty-five combined segmental and wedge resections with reconstitution, and a similar group of 223 cases without reconstitution have been analyzed as to postoperative complications as determined by the incidence of space problems, fistulas, empyemas, and occult fistulas. A smaller group of pure segmental resections has been similarly studied.

2. It has been shown that there is a significantly higher incidence of major complications and space problems in segmental resections without reconstitution.

3. A large percentage of the complications encountered occurred in the presence of good chemotherapy coverage and were due to infection with secondary organisms.

4. The conclusion is drawn that the anatomic situation, comprising the conical segmental defect with raw lung surface exposed to pleural cavity, plus secondary, contamination from air leaks, is favorable to the development of secondary infections and should therefore be avoided.

5. Reconstitution of raw lung surfaces presents a method of avoiding the undesirable anatomic situation, of reducing serious air leaks and, therefore, markedly reduces the incidence of serious postoperative complications.

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BRONCHOGENIC CARCINOMA: COMPARISON OF NATURAL COURSE AND TREATMENT WITH RESECTION, X-RADIATION, AND NITROGEN MUSTARD

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THIS is a report of a group of 547 consecutive proved bronchogenic carcinomas in patients who have all been followed for 6 months to 12 years. This series is unusual because the 30-day mortality after resection was less than 3 per cent, because lobectomy was almost as frequent as pneumonectomy, and because 37 per cent of the patients subjected to resection and over 10 per cent of all patients were alive 5 years after proved diagnosis. Meade and co-workers,[1] in 1946, reported the experiences with lobectomy from one of the Army's larger chest surgical centers and this service has been continued by the Veterans Administration at Kennedy Hospital. The authors believe that this extensive background of chest specialization and continuation of full-time interest is responsible for this series of patients.

TABLE I. PRESENTING SYMPTOMS

SYMPTOM	PER CENT OF CASES	DURATION BEFORE HOSPITALIZATION		
		0 TO 3 MO. (%)	MORE THAN 24 MO. (%)	AVERAGE (MO.)
Cough	65.2	35.8	18.5	7.8
Gross bleeding	35.6	29.9	21.8	11.0
Chest pain	37.1	38.4	13.7	8.6
Weight loss	34.4	36.0	12.8	7.7
Dyspnea	24.6	33.9	26.0	11.6
Fever	11.6	48.3	8.3	9.9
Weakness	8.1	52.4	9.5	6.7
Routine x-ray	7.3	—	—	—
Joint pains	7.0	—	—	—
Hoarseness	5.0	—	—	—
Pneumonia	5.0	—	—	—
Palpable masses	4.0	—	—	—
Back pain	3.0	—	—	—
Wheezing	3.0	—	—	—

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DIAGNOSIS

The occurrence of various presenting symptoms is shown in Table I. Over 60 per cent of the group experienced symptoms more than 3 months before hospitalization.

Twenty-one per cent of the patients showed no abnormalities on physical examination at the time of admission. An additional 34 per cent showed no significant abnormalities outside the chest.

The admission x-ray findings are reported in Table II. Only 7 per cent of the lesions were less than 3 cm. in diameter, and 73 per cent were over 6 cm. in diameter.

TABLE II. X-RAY FINDINGS ON ADMISSION (523 CASES)

			NUMBER	PER CENT
Mass in lung			222	42.4
(a) Multiple	20	3.8%		
(b) "Pancoasts"	8	1.5%		
Hilar mass			115	22.0
"Soft" infiltrates			84	16.1
Atelectasis			62	11.9
Effusion			52	9.9
Rib erosion			27	5.2
Cavity in lung			22	4.2
Negative			19	3.6
Emphysema, only			16	3.1
Diaphragm, elevation			15	2.9
Pleural thickening			6	1.1
Spine erosion, only			3	0.6

The diagnosis was proved by surgery in 38 per cent, by bronchoscopy in 29 per cent, at autopsy in 20 per cent (not suspected prior to death in 6 per cent), and by supraclavicular node dissection in 13 per cent.

Supraclavicular node dissections were performed on more than 100 patients, but gave histologic proof of cancer in only 20 per cent of these cases. When palpable nodes were absent, the procedure was of little help in making the diagnosis.

Cytologic examination of the sputum was disappointing as a diagnostic aid during its first few years of use. However, analysis of the results in the last 2 years reveals 81 per cent accuracy with only 4 per cent false positives.

It was difficult, in many cases, to differentiate a metastic cancer from a primary bronchogenic carcinoma. In 15 cases in which a diagnosis of metastatic tumor was made, autopsy revealed the pulmonary mass to be a primary bronchogenic carcinoma. In 20 additional cases, the clinical diagnosis of tuberculosis, pneumonia, or brain tumor was proved by autopsy to be bronchogenic cancer.

SELECTION FOR SURGERY

The most important factor affecting the operative mortality rate and 5-year survival is the selection of patients for surgery with localized or relatively controlled cancer.

A 1- to 2-week period of observation allows many suspected cases to be excluded from surgery due to clearing of the lesion or to detection of previously obscure metastasis. After cancer has metastasized, any surgical procedure is usually futile, offers false hope to the patient and family, and is unnecessarily derogatory of definitive surgery due to the associated high operative mortality rate or early death of the patient.

We have consistently recommended resection of pulmonary lesions after failure of diagnosis or medical therapy. This has resulted in many cases, in the removal of very early tumors. Several lobes removed for chronic inflammatory disease have revealed carcinoma, almost of the in situ type.

Contraindications to surgery included obviously terminal cases (15.4 per cent), distant metastases (23.9 per cent), local extension (16.6 per cent), to heart, brachial plexus, ribs, trachea (1.8 per cent), and diaphragm (1.3 per cent), or malignant effusions (2.2 per cent). A few patients refused surgery (0.9 per cent).

Tumor invasion of the left recurrent nerve or either phrenic nerve was present in some patients in whom the lesion remained localized to an area which could be completely resected. Occasionally, these patients survived over 5 years.

Realization that surgery offered a fair hope of cure and a low mortality led to broadening the criteria for operation and a willingness to offer resection to all patients without clear-cut evidence of incurability. Forty-one per cent of all patients were operated upon.

SURGERY

One hundred thirty-seven patients had pulmonary resections (60.3 per cent of the operated cases, 25 per cent of all cases). Squamous carcinomas were found the most likely to be resectable, and alveolar cell carcinomas least likely (Table III). We prefer to perform resections in all cases possible since it is not apparent from clinical studies which patients may be cured and which will obtain only palliation.

TABLE III. HISTOLOGY

CELL TYPE	NUMBER OF CASES	PER CENT TOTAL CASES	PER CENT OPERABLE	PER CENT RESECT-ABLE	5-YEAR SURVIVAL		
					RESECTED CASES	ALL CASES	
Anaplastic	193	35.3	42.5	46	21	(4/74)	5.4
Squamous	169	30.9	39.4	78	42	(10/70)	14.3
Poorly differentiated bronchogenic	120	21.9	34.0	66	47	(7/81)	8.6
Adenocarcinoma	55	10.1	58.0	50	30	(3/40)	7.5
Alveolar	10	1.8	40 0	20	0	(0/2)	0.0
Totals	547	100	41.4	60	37	(24/267)	9.0

After lobectomy or pneumonectomy, the mediastinum is now dissected and all obvious lymph nodes removed, but this was not always done. Intrapericardial dissection of the vessels was frequent, although not routine. Lobectomy has

TABLE IV

TREATMENT	ALL CASES				CASES SEEN OVER FIVE YEARS AGO			
	NUMBER OF CASES	NUMBER ALIVE	PER CENT ALIVE	MEAN FOLLOW-UP MO.	NUMBER OF CASES	NO. ALIVE MORE THAN 5 YEARS	PER CENT ALIVE MORE THAN 5 YEARS	MEAN SURVIVAL OF PATIENTS WHO DIED IN LESS THAN 5 YR.
*Pneumonectomies**								
Curative	32	14	44	54.1	19	11	58	13.7
Palliative	23	17	74	29.0	18	3	17	11.6
Totals	55	31	56	43.7	37	14	38	12.5
*Lobectomies**								
Curative	18	11	61	41.6	8	6	75	14.7
Palliative	27	4	15	9.5	14	2	14	13.0
Totals*	45	15	33	33.7	22	8	36	13.7
Segmental	2	0	0	—	2	0	0	28.0
Exploratory only	17	0	0	0.0	9	0	0	3.8
Exploratory plus x-ray and/or mustard	73	8	11	23.0	43	1	2	11.6
Totals	90	8	9	23.0	52	1	2	8.2
Nitrogen mustard	21	2	9.5	4.1	5	0	0	7.4
X-ray	161	20	12	12.6	73	0	0	9.4
X-ray and mustard	30	2	7	18.7	8	0	0	8.1
No treatment	108	0	0	81.0	68	1	1	6.9
Totals	320	24	7.5	29.0	154	1	.3	7.9
Grand totals	512	78	15.2		267	24	9.0	8.3

*Pulmonary resections performed elsewhere but with the patients treated here later are *not* included.

been consistently preferred because of the marked disability noted in healthy young patients subjected to pneumonectomy before 1945. Our results following lobectomy done before 1952 were good (36 per cent 5-year survival). This finding led us to extend the indications for lobectomy in the next 2 years with a marked drop in the survival rate.

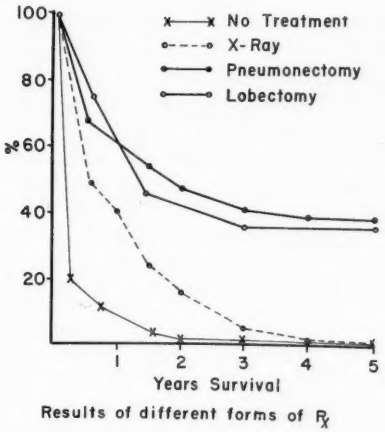

Fig. 1.—Results of various forms of treatment in improving the prognosis of patients with cancer of the lung.

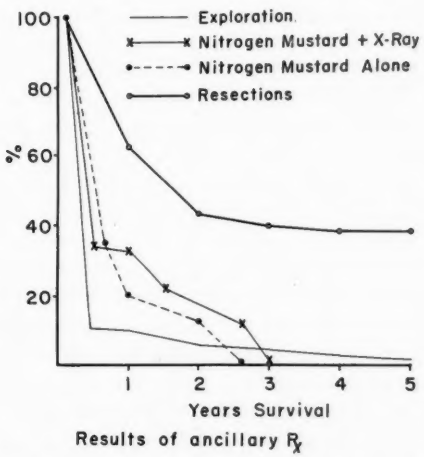

Fig. 2.—Survival of patients receiving different forms of treatment.

The operating room mortality was 1.8 per cent for pneumonectomy (0 in the last 10 years) and 0 per cent for lobectomy. No other patient having pneumonectomy died within 30 days of surgery, but 2 of those having lobectomy died. The causes of death were metastatic cancer and cerebrovascular accident.

ANCILLARY THERAPY (Figs. 1 and 2)

If there was doubt of complete removal of all tumor by the resection, nitrogen mustard and/or x-radiation was also given. These agents were given to 23 patients (42 per cent) having pneumonectomy and to 27 patients (60 per cent) having lobectomy on our service.

We are currently in a cooperative study on the effects of simultaneous chemotherapy and surgery. None of the cases placed on these protocols has been included in this report.

Of the patients explored without resection, 73 (81 per cent) received x-radiation mustard therapy or both. There was apparently some favorable effect from these agents in this group.

One hundred and eight patients (19.7 per cent) were given no specific cancer therapy. This group included a few patients who refused all aid, as well as the obviously terminal cases.

When cure is not possible, we employ an aggresive approach aimed at giving a maximum enjoyment of remaining life. Tranquilizers, adequate feeding, x-radiation, and chemotherapy are used to the maximal extent and as often as possible. These agents are not withheld until needed for pain control.

RESULTS

Survival time (Figs. 1 and 2, and Table IV) was considered to be from the time of original admission to the hospital to death, unless the patient was operated upon, in which case it was from the day of surgery to death.

"Curative" resections are those in which the staff did not use x-radiation or nitrogen mustard within the first 3 months following surgery, and "palliative" are those who were given x-radiation or nitrogen mustard during the postoperative period. The decision to use x-radiation therapy is based on many factors, such as the microscopic appearance of the lymph nodes, proximity of tumor to lines of resection, invasion of vessels, etc.

It is apparent that in those cases in which x-radiation and/or mustard therapy was selected, the choice was appropriate, since the 5-year survival rate was only about 15 per cent as opposed to the 63 per cent rate in those cases in which these agents were not employed. Of course, metastases which became apparent and were treated within 3 months of surgery could bias these data in favor of the "curative" resections. While this did occur, it was not common.

It is possible to obtain as satisfactory results with lobectomy as with pneumonectomy in properly selected cases.

Factors which influenced the decision to do a lobectomy included: absence of involvement of primary or intermediate bronchi, main pulmonary artery, or fissure; peripheral location, particularly in the upper lobes; and poor pulmonary reserve (by clinical estimation).

Table IV shows that exploration followed by x-radiation and/or nitrogen mustard therapy gave results which were better than no treatment and in the same range as x-ray therapy alone.

Nitrogen mustard has been used in 96 cases in this group: in 21 as the sole therapy, in 30 in conjunction with x-ray therapy, in 21 of exploration,

and in 24 of resection. The survival data do not reveal an effect from the drug; however, our clinical feeling is quite the contrary. In a few incidences, the response to nitrogen mustard has been gratifying.

X-ray therapy was used as the sole specific treatment in 161 cases and in conjunction with other modes of therapy in 166 additional cases for a total of 327 cases (73 per cent of the series). When used alone, the 5-year survival rate was 0 and the mean survival time was only 9.4 months. However (Fig. 1), x-ray therapy offers a clear-cut increase in the probability of living between 1 and 2 years, aside from palliation.

Since many of our patients were transferred to us from other hospitals, and these data are biased due to referral for terminal care or x-radiation therapy, we have made a separate analysis of patients who were admitted first to our hospital.

Results in Kennedy Patients.—Excluding the 53 cases transferred here for terminal care, and the 67 patients operated upon elsewhere before referral, there remained 427 patients who were either available for therapy or were seen for the first admission at our hospital. Of these 427 cases, 209 were admitted over 5 years ago.

In 136 cases there was no evidence of extension or metastasis at the time of entering the hospital. Twenty-three of these patients were alive 5 years after admission. This gives a 5-year survival rate of 16.9 per cent for those patients admitted before obvious signs and symptoms of extension or metastasis had become apparent. The 5-year survival rate of *all* patients admitted originally to this hospital is 11.5 per cent (24/209).

We have complete information in 371 cases as to sites of extension. The parietal pleura was invaded by direct extension in 59 cases (15.9 per cent). The ribs were involved in 43 patients (11.6 per cent), pericardium in 28 (7.5 per cent), other lung in 3.5 per cent, heart in 2.7 per cent, superior vena cava in 1.9 per cent, aorta in 1.9 per cent, and esophagus in 1.3 per cent.

Sites of metastasis are shown in Table V. It is seen that the retroperitoneal structures, i.e., adrenals, liver, kidneys, and pancreas, were frequently involved. This may be accounted for by the direct lymphatic connections from the lung

TABLE V. SITES OF METASTASIS (274 COMPLETE AUTOPSIES)

	NO. OF CASES	PER CENT		NO. OF CASES	PER CENT
Mediastinal nodes	157	57.3			
Adrenals	113	41.2	Spleen	34	12.4
Bone	101	36.9	Gut	25	9.1
Liver	89	32.5	Thyroid	18	6.6
Kidney	63	23.0	Skin	14	5.1
Lung	58	21.2	Prostate	4	1.5
Brain	50	18.2	Gall bladder	3	1.1
Heart	43	15.7	Pituitary	3	1.1
None	37	13.5	Bladder	1	0.4
Pancreas	36	13.1	Testis	1	0.4

to this region. The high rate of involvement of the adrenals should always be kept in mind when shock persists after surgery. Practically no structure in the body is immune to metastatic implants.

SUMMARY

1. Five hundred forty-seven consecutive proved cases of bronchogenic carcinoma with follow-up of all patients are analyzed. The median age was 58 years.

2. The average duration of symptoms before hospitalization was over 8 months, and 16 per cent of the patients had symptoms over 2 years before being admitted. Seven per cent of the patients had abnormal routine chest x-ray studies in the absence of symptoms; 65 per cent had a mass demonstrated on roentgenograms of the chest, and these masses exceeded 6 cm. in diameter in 73 per cent of cases.

3. The operability rate was 41.4 per cent of all patients admitted; the resectability rate was 60.3 per cent of those patients operated upon.

4. Lobectomy *in properly selected cases* gave results comparable to pneumonectomy. The operating room mortality was less than 1 per cent, and the 30-day mortality slightly over 2 per cent.

5. The 5-year survival rate after resection was 37 per cent.

6. High voltage x-radiation and nitrogen mustard therapy earned a place in prolonging useful life and in palliation.

7. The 5-year survival rate of *all* patients with bronchogenic carcinoma originally admitted to this hospital was 11.5 per cent (24/209).

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